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(54) Title: DIPEPTIDYL PEPTIDASES

(57) Abstract: Peptides which comprise sequences as shown in Seq ID NO:2 or HisGlyTrpSerTypGlyGlyPheLeu; LeuAspGluAsnValHisPhePhe; GluArgHisSerIleArg and PheValIleGlnGluGluPhe which show peptidase ability and have substrate specificity for at least one of the compounds H-Ala-Pro-pNA, H-Gly-Pro-pNA, H-Gly-Pro-pNA ans H-Arg-Pro-pNA. peptides having sequence ID No:7 are also claimed. Nucleic acids, vectors, antibodies and hybridoma cells are also claimed with reference to the above sequences and there abilities.

TITLE

DIPEPTIDYL PEPTIDASES

FIELD OF INVENTION

The invention relates to a dipeptidyl peptidase, to a nucleic acid molecule which encodes it, and to uses of the peptidase.

BACKGROUND OF THE INVENTION

The dipeptidyl peptidase (DPP) IV-like gene family is a family of molecules which have related protein structure and function [1-3]. The gene family includes the following molecules: DPPIV (CD26), dipeptidyl amino-peptidase-like protein 6 (DPP6), dipeptidyl amino-peptidase-like protein 8 (DPP8) and fibroblast activation protein (FAP) [1,2,4,5]. Another possible member is DPPIV-β[6].

The molecules of the DPPIV-like gene family are serine proteases, they are members of the peptidase family S9b, and together with prolyl endopeptidase (S9a) and acylaminoacyl peptidase (S9c), they are comprised in the prolyl oligopeptidase family[5,7].

DPPIV and FAP both have similar postproline dipeptidyl amino peptidase activity, however, unlike DPPIV, FAP also has gelatinase activity[8,9].

DPPIV substrates include chemokines such as RANTES, eotaxin, macrophage-derived chemokine and stromal-cell-derived factor 1; growth factors such as glucagon and glucagon-like peptides 1 and 2; neuropeptides including neuropeptide Y and substance P; and vasoactive peptides[10-12].

DPPIV and FAP also have non-catalytic activity; DPPIV binds adenosine deaminase, and FAP binds to $\alpha_3\beta_1$ and $\alpha_5\beta_1$ integrin[13-14].

In view of the above activities, the DPPIV-like family members are likely to have roles in intestinal and renal handling of proline containing peptides, cell adhesion, peptide metabolism, including metabolism of cytokines, neuropeptides, growth factors and chemokines, and immunological processes, specifically T cell stimulation[3,11,12].

Consequently, the DPPIV-like family members are likely to be involved in the pathology of disease, including for example, tumour growth and biology, type II diabetes, cirrhosis, autoimmunity, graft rejection and HIV infection[3,15-18].

Inhibitors of DPPIV have been shown to suppress arthritis, and to prolong cardiac allograft survival in animal models *in vivo*[19,20]. Some DPPIV inhibitors are reported to inhibit HIV infection[21]. It is anticipated that DPPIV inhibitors will be useful in other therapeutic applications including treating diarrhoea, growth hormone deficiency, lowering glucose levels in non insulin dependent diabetes mellitus and other disorders involving glucose intolerance, enhancing mucosal regeneration and as immunosuppressants[3,21-24].

There is a need to identify members of the DPPIV-like gene family as this will allow the identification of inhibitor(s) with specificity for particular family member(s), which can then be administered for the purpose of treatment of disease. Alternatively, the identified member may of itself be useful for the treatment of disease.

SUMMARY OF THE INVENTION

The present invention seeks to address the above identified need and in a first aspect provides a peptide which comprises the amino acid sequence shown in SEQ ID NO:2.

As described herein, the inventors believe that the peptide is a prolyl oligopeptidase and a dipeptidyl peptidase, because it has substantial and significant homology with the amino acid sequences of DPPIV and DPP8. As homology is observed between DPP8, DPPIV and DPP9, it will be understood that DPP9 has a substrate specificity for at least one of the following compounds: H-Ala-Pro-pNA, H-Gly-Pro-pNA and H-Arg-Pro-pNA.

The peptide is homologous with human DPPIV and DPP8, and importantly, identity between the sequences of DPPIV and DPP8 and SEQ ID NO: 2 is observed at the regions of DPPIV and DPP8 containing the catalytic triad residues and the two glutamate residues of the β-propeller domain essential for DPPIV enzyme activity. The observation of amino acid sequence homology means that the peptide which has the amino acid sequence shown in SEQ ID NO:2 is a member of the DPPIV-like gene family. Accordingly the peptide is now named and described herein as DPP9.

The following sequences of the human DPPIV amino acid sequence are important for the catalytic activity of DPPIV: (i) Trp^{617}GlyTrpSerTyrGlyGlyTyrVal; (ii) Ala^{707}AspAspAsnValHisPhe; (iii) Glu^{738}AspHisGlyIleAlaSer; and (iv) Trp^{201}ValTyrGluGluGluVal [25-28]. As described herein, the alignment of the following sequences of DPP9: His^{833}GlyTrpSerTyrGlyGlyPheLeu; Leu^{913}AspGluAsnValHisPhePhe; Glu^{944}ArgHisSerIleArg and Phe^{350}ValIleGlnGluGluPhe with sequences (i) to (iv) above, respectively, suggests that these sequences of DPP9 are likely to confer the catalytic activity of DPP9. This is also supported by the alignment of DPP9 and DPP8 amino acid sequences. More specifically, DPP8 has substrate specificity for H-Ala-Pro-pNA, H-Gly-Pro-pNA and H-Arg-Pro-pNA, and shares near identity, with only one position of amino acid difference, in each of the above described sequences of DPP9. Thus, in a second aspect, the invention provides a peptide comprising the following amino acid sequences:

HisGlyTrpSerTyrGlyGlyPheLeu; LeuAspGluAsnValHisPhePhe; GluArgHisSerIleArg and PheValIleGlnGluGluPhe; which has the substrate specificity of the sequence shown in SEQ ID NO:2.

Also described herein, using the GAP sequence alignment algorithm, it is observed that DPP9 has 53% amino acid similarity and 29% amino acid identity with a *C. elegans* protein. Further, as shown herein, a nucleic acid molecule which encodes DPP9, is capable of hybridising specifically with DPP9 sequences derived from non-human species, including rat and mouse. Further, the inventors have isolated and characterised a mouse homologue of human DPP9. Together these data demonstrate that DPP9 is expressed in non-human species. Thus in a third aspect, the invention provides a peptide which has at least 91% amino acid identity with the amino acid sequence shown in SEQ ID NO:2, and which has the substrate specificity of the sequence shown in SEQ ID NO:2. Typically the peptide has the sequence shown in SEQ ID NO:4. Preferably, the amino acid identity is 75%. More preferably, the amino acid identity is 95%. Amino acid identity is calculated using GAP software [GCG Version 8, Genetics Computer Group, Madison, WI, USA] as described further herein. Typically, the peptide comprises the following sequences: HisGlyTrpSerTyrGlyGlyPheLeu; LeuAspGluAsnValHisPhePhe; GluArgHisSerIleArg and PheValIleGlnGluGluPhe.

In view of the homology between DPPIV, DPP8 and DPP9 amino acid sequences, it is expected that these sequences will have similar tertiary structure. This means that the tertiary structure of DPP9 is likely to include the seven-blade β- propeller domain and the α/β hydrolase domain of DPPIV. These structures in DPP9 are likely to be conferred by the regions comprising β-propeller, Val^{226} to Ala^{705}, α/β hydrolase, Ser^{706} to Leu^{969} and about 70 to 90 residues in the region Ser^{136} to Gly^{225}. As it is known that the β-propeller domain regulates proteolysis mediated by the catalytic triad in the α/β hydrolase domain of prolyl

oligopeptidase, [29] it is expected that truncated forms of DPP9 can be produced, which have the substrate specificity of the sequence shown in SEQ ID NO:2, comprising the regions referred to above (His^{833}GlyTrpSerTyrGlyGlyPheLeu; Leu^{913}AspGluAsnValHisPhePhe; Glu^{944}ArgHisSerIleArg and Phe^{350}ValIleGlnGluGluPhe) which confer the catalytic specificity of DPP9. Examples of truncated forms of DPP9 which might be prepared are those in which the region conferring the β-propeller domain and the α/β hydrolase domain are spliced together. Other examples of truncated forms include those that are encoded by splice variants of DPP9 mRNA. Thus although, as described herein, the biochemical characterisation of DPP9 shows that DPP9 consists of 969 amino acids and has a molecular weight of about 110 kDa, it is recognised that truncated forms of DPP9 which have the substrate specificity of the sequence shown in SEQ ID NO:2, may be prepared using standard techniques [30,31]. Thus in a fourth aspect, the invention provides a fragment of the sequence shown in SEQ ID NO: 2, which has the substrate specificity of the sequence shown in SEQ ID NO:2. The inventors believe that a fragment from Ser136 to Leu969 (numbered according to SEQ ID NO:2) would have enzyme activity.

It is recognised that DPP9 may be fused, or in other words, linked to a further amino acid sequence, to form a fusion protein which has the substrate specificity of the sequence shown in SEQ ID NO:2. An example of a fusion protein is one which comprises the sequence shown in SEQ ID NO:2 which is linked to a further amino acid sequence: a "tag" sequence which consists of an amino acid sequence encoding the V5 epitope and a His tag. An example of another further amino acid sequence which may be linked with DPP9 is a glutathione S transferase (GST) domain [30]. Another example of a further amino acid sequence is a portion of CD8α [8]. Thus in one aspect, the invention provides a fusion protein comprising the amino acid sequence shown in

SEQ ID NO:2 linked with a further amino acid sequence, the fusion protein having the substrate specificity of the sequence shown in SEQ ID NO:2.

It is also recognised that the peptide of the first aspect of the invention may be comprised in a polypeptide, so that the polypeptide has the substrate specificity of DPP9. The polypeptide may be useful, for example, for altering the protease susceptibility of DPP9, when used in *in vivo* applications. An example of a polypeptide which may be useful in this regard, is albumin. Thus in another embodiment, the peptide of the first aspect is comprised in a polypeptide which has the substrate specificity of DPP9.

In one aspect, the invention provides a peptide which includes the amino acid sequence shown in SEQ ID NO:7. In one embodiment the peptide consists of the amino acid sequence shown in SEQ ID NO:7.

As described further herein, the amino acid sequence shown in SEQ ID NO:7, and the amino acid sequences of DPPIV, DPP8 and FAP are homologous. DPPIV, DPP8 and FAP have dipeptidyl peptidase enzymatic activity and have substrate specificity for peptides which contain the di-peptide sequence, Ala-Pro. The inventors note that the amino acid sequence shown in SEQ ID NO:7 contains the catalytic triad, Ser-Asp-His. Accordingly, it is anticipated that the amino acid sequence shown in SEQ ID NO:7 has enzymatic activity in being capable of cleaving a peptide which contains Ala-Pro by hydrolysis of a peptide bond located C-terminal adjacent to proline in the di-peptide sequence.

In one embodiment, the peptide comprises an amino acid sequence shown in SEQ ID NO:7 which is capable of cleaving a peptide bond which is C-terminal adjacent to proline in the sequence Ala-Pro. The capacity of a dipeptidyl

peptidase to cleave a peptide bond which is C-terminal adjacent to proline in the di-peptide sequence Ala-Pro can be determined by standard techniques, for example, by observing hydrolysis of a peptide bond which is C-terminal adjacent to proline in the molecule Ala-Pro-p-nitroanilide.

The inventors recognise that by using standard techniques it is possible to generate a peptide which is a truncated form of the sequence shown in SEQ ID NO:7, which retains the proposed enzymatic activity described above. An example of a truncated form of the amino acid sequence shown in SEQ ID NO:7 which retains the proposed enzymatic activity is a form which includes the catalytic triad, Ser-Asp-His. Thus a truncated form may consist of less than the 831 amino acids shown in SEQ ID NO:7. Accordingly, in a further embodiment, the peptide is a truncated form of the peptide shown in SEQ ID NO:7, which is capable of cleaving a peptide bond which is C-terminal adjacent to proline in the sequence Ala-Pro.

It will be understood that the amino acid sequence shown in SEQ ID NO:7 may be altered by one or more amino acid deletions, substitutions or insertions of that amino acid sequence and yet retain the proposed enzymatic activity described above. It is expected that a peptide which is at least 47% similar to the amino acid sequence of SEQ ID NO:7, or which is at least 27% identical to the amino acid sequence of SEQ ID NO:7, will retain the proposed enzymatic activity described above. The % similarity can be determined by use of the program/algorithm "GAP" which is available from Genetics Computer Group(GCG),Wisconsin. Thus in another embodiment of the first aspect, the peptide has an amino acid sequence which is at least 47% similar to the amino acid sequence shown in SEQ ID NO:7, and is capable of cleaving a peptide bond which is C-terminal adjacent to proline in the sequence Ala-Pro.

As described above, the isolation and characterisation of DPP9 is necessary for identifying inhibitors of DPP9 catalytic activity, which may be useful for the treatment of disease. Accordingly, in a fifth aspect, the invention provides a method of identifying a molecule capable of inhibiting cleavage of a substrate by DPP9, the method comprising the following steps:

(a) contacting DPP9 with the molecule;

(b) contacting DPP9 of step (a) with a substrate capable of being cleaved by DPP9, in conditions sufficient for cleavage of the substrate by DPP9; and

(c) detecting substrate not cleaved by DPP9, to identify that the molecule is capable of inhibiting cleavage of the substrate by DPP9.

It is recognised that although inhibitors of DPP9 may also inhibit DPPIV and other serine proteases, as described herein, the alignment of the DPP9 amino acid sequence with most closely related molecules, (i.e. DPPIV), reveals that the DPP9 amino acid is distinctive, particularly at the regions controlling substrate specificity. Accordingly, it is expected that it will be possible to identify inhibitors which inhibit DPP9 catalytic activity specifically, which do not inhibit catalytic activity of DPPIV-like gene family members, or other serine proteases. Thus, in a sixth aspect, the invention provides a method of identifying a molecule capable of inhibiting specifically, the cleavage of a substrate by DPP9, the method comprising the following steps:

(a) contacting DPP9 and a further protease with the molecule;

(b) contacting DPP9 and the further protease of step (a) with a substrate capable of being cleaved by DPP9 and the further protease, in conditions sufficient for cleavage of the substrate by DPP9 and the further protease; and

(c) detecting substrate not cleaved by DPP9, but cleaved by the further protease, to identify that the molecule is capable of inhibiting specifically, the cleavage of the substrate by DPP9.

In a seventh aspect, the invention provides a method of reducing or inhibiting the catalytic activity of DPP9, the method comprising the step of contacting DPP9 with an inhibitor of DPP9 catalytic activity. In view of the homology between DPP9 and DPP8 amino acid sequences, it will be understood that inhibitors of DPP8 activity may be useful for inhibiting DPP9 catalytic activity. Examples of inhibitors suitable for use in the seventh aspect are described in [21,32,33]. Other inhibitors useful for inhibiting DPP9 catalytic activity can be identified by the methods of the fifth or sixth aspects of the invention.

In one embodiment, the catalytic activity of DPP9 is reduced or inhibited in a mammal by administering the inhibitor of DPP9 catalytic activity to the mammal. It is recognised that these inhibitors have been used to reduce or inhibit DPPIV catalytic activity *in vivo*, and therefore, may also be used for inhibiting DPP9 catalytic activity *in vivo*. Examples of inhibitors useful for this purpose are disclosed in the following [21,32-34].

Preferably, the catalytic activity of DPP9 in a mammal is reduced or inhibited in the mammal, for the purpose of treating a disease in the mammal. Diseases which are likely to be treated by an inhibitor of DPP9 catalytic activity are those in which DPPIV-like gene family members are associated [3,10,11,17,21,36], including for example, neoplasia, type II diabetes, cirrhosis, autoimmunity, graft rejection and HIV infection.

Preferably, the inhibitor for use in the seventh aspect of the invention is one which inhibits the cleavage of a peptide bond C-terminal adjacent to proline. As described

herein, examples of these inhibitors are 4-(2-aminoethyl)benzenesulfonylfluoride, aprotinin, benzamidine/HCl, Ala-Pro-Gly, H-Lys-Pro-OH HCl salt and zinc ions, for example, zinc sulfate or zinc chloride. More preferably, the inhibitor is one which specifically inhibits DPP9 catalytic activity, and which does not inhibit the catalytic activity of other serine proteases, including, for example DPPIV, DPP8 or FAP.

In an eighth aspect, the invention provides a method of cleaving a substrate which comprises contacting the substrate with DPP9 in conditions sufficient for cleavage of the substrate by DPP9, to cleave the substrate. Examples of molecules which can be cleaved by the method are H-Ala-Pro-pNA, H-Gly-Pro-pNA and H-Arg-Pro-pNA. Molecules which are cleaved by DPPIV including RANTES, eotaxin, macrophage-derived chemokine, stromal-cell-derived factor 1, glucagon and glucagon-like peptides 1 and 2, neuropeptide Y, substance P and vasoactive peptide are also likely to be cleaved by DPP9 [11,12]. In one embodiment, the substrate is cleaved by cleaving a peptide bond C-terminal adjacent to proline in the substrate. The molecules cleaved by DPP9 may have Ala, or Trp, Ser, Gly, Val or Leu in the P1 position, in place of Pro [11,12].

The inventors have characterised the sequence of a nucleic acid molecule which encodes the amino acid sequence shown in SEQ ID NO:2. Thus in a tenth aspect, the invention provides a nucleic acid molecule which encodes the amino acid sequence shown in SEQ ID NO:2.

In an eleventh aspect, the invention provides a nucleic acid molecule which consists of the sequence shown in SEQ ID NO:1.

In another aspect, the invention provides a nucleic acid molecule which encodes a peptide comprising the amino acid sequence shown in SEQ ID NO:7.

The inventors have characterised the nucleotide sequence of the nucleic acid molecule encoding SEQ ID NO:7. The nucleotide sequence of the nucleic acid molecule encoding DPP4-like-2 is shown in SEQ ID NO:8. Thus, in one embodiment, the nucleic acid molecule comprises the nucleotide sequence shown in SEQ ID NO:8. In another embodiment, the nucleic acid molecule consists of the nucleotide sequence shown in SEQ ID NO:8.

The inventors recognise that a nucleic acid molecule which has the nucleotide sequence shown in SEQ ID NO:8 could be made by producing only the fragment of the nucleotide sequence which is translated. Thus in an embodiment, the nucleic acid molecule does not contain 5′ or 3′ untranslated nucleotide sequences.

As described herein, the inventors observed RNA of 4.4 kb and a minor band of 4.8 kb in length which hybridised to a nucleic acid molecule comprising sequence shown in SEQ ID NO:8. It is possible that these mRNA species are splice variants. Thus in another embodiment, the nucleic acid molecule comprises the nucleotide sequence shown in SEQ ID NO:8 and which is approximately 4.4 kb or 4.8 kb in length.

In another embodiment, the nucleic acid molecule is selected from the group of nucleic acid molecules consisting of DPP4-like-2a, DPP4-like-2b and DPP4-like-2c, as shown in Figure 2.

In another aspect, the invention provides a nucleic acid molecule having a sequence shown in SEQ ID NO: 3.

In a twelfth aspect, the invention provides a nucleic acid molecule which is capable of hybridising to a nucleic acid molecule consisting of the sequence shown in SEQ ID NO:1 in stringent conditions, and which encodes a peptide which has the substrate specificity of the sequence shown in SEQ ID NO:2. As shown in the Northern blot analysis described herein, DPP9 mRNA hybridises specifically to the sequence shown in SEQ ID NO:1, after washing in 2XSSC/ 1.0%SDS at 37°C, or after washing in 0.1XSSC/0.1% SDS at 50°C. "Stringent conditions" are conditions in which the nucleic acid molecule is exposed to 2XSSC/ 1.0% SDS. Preferably, the nucleic acid molecule is capable of hybridising to a molecule consisting of the sequence shown in SEQ ID NO:1 in high stringent conditions. "High stringent conditions" are conditions in which the nucleic acid molecule is exposed to 0.1XSSC/ 0.1%SDS at 50°C.

As described herein, the inventors believe that the gene which encodes DPP9 is located at band p13.3 on human chromosome 19. The location of the DPP9 gene is distinguished from genes encoding other prolyl oligopeptidases, which are located on chromosome 2, at bands 2q24.3 and 2q23, chromosome 7 or chromosome 15q22. Thus in an embodiment, the nucleic acid molecule is one capable of hybridising to a gene which is located at band p13.3 on human chromosome 19.

It is recognised that a nucleic acid molecule which encodes the amino acid sequence shown in SEQ ID NO:2, or which comprises the sequence shown in SEQ ID NO:1, could be made by producing the fragment of the sequence which is translated, using standard techniques [30,31]. Thus in an embodiment, the nucleic acid molecule does not contain 5' or 3' untranslated sequences.

In a thirteenth aspect, the invention provides a vector which comprises a nucleic acid molecule of the tenth aspect of the invention. In one embodiment, the vector is capable of replication in a COS-7 cell, CHO cell or 293T cell, or E.coli. In another embodiment, the vector is selected from the group consisting of λTripleEx, pTripleEx, pGEM-T Easy Vector, pSecTag2Hygro, pet15b, pEE14.HCMV.gs and pCDNA3.1/V5/His.

In a fourteenth aspect, the invention provides a cell which comprises a vector of the thirteenth aspect of the invention. In one embodiment, the cell is an E.coli cell. Preferably, the E. coli is MC1061, DH5α, JM109, BL21DE3, pLysS. In another embodiment, the cell is a COS-7, COS-1, 293T or CHO cell.

In a fifteenth aspect, the invention provides a method for making a peptide of the first aspect of the invention comprising, maintaining a cell according to the fourteenth aspect of the invention in conditions sufficient for expression of the peptide by the cell. The conditions sufficient for expression are described herein. In one embodiment, the method comprises the further step of isolating the peptide.

In a sixteenth aspect, the invention provides a peptide when produced by the method of the fifteenth aspect.

In a seventeenth aspect, the invention provides a composition comprising a peptide of the first aspect and a pharmaceutically acceptable carrier.

In an eighteenth aspect, the invention provides an antibody which is capable of binding a peptide according to the first aspect of the invention. The antibody can be

prepared by immunising a subject with purified DPP9 or a fragment thereof according to standard techniques [35]. An antibody may be prepared by immunising with transiently transfected DPP9$^+$ cells. It is recognised that the antibody is useful for inhibiting activity of DPP9. In one embodiment, the antibody of the eighteenth aspect of the invention is produced by a hybridoma cell.

In a nineteenth aspect, the invention provides a hybridoma cell which secretes an antibody of the nineteenth aspect.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1. Nucleotide sequence of DPP8 (SEQ ID NO:5).

Figure 2. Schematic representation of the cloning of human cDNA DPP9.

Figure 3. Schematic representation of the assembly of nucleotide sequences of human cDNA DPP9.

Figure 4. Nucleotide sequence of human cDNA DPP9 (SEQ ID NO:1) and amino acid sequence of human DPP9 (SEQ ID NO:2).

Figure 5. Alignment of human DPP9 amino acid sequences with the amino acid sequence encoded by a predicted open reading frame of GDD.

Figure 6. Alignment of human DPP8, DPP9, DPP4 and FAP amino acid sequences.

Figure 7. Northern blot analysis of human DPP9 RNA.

Figure 8. Alignment of murine (SEQ ID NO:4) and human DPP9 amino acid sequences.

Figure 9. Alignment of murine (SEQ ID NO:3) and human DPP9 cDNA nucleotide sequences.

Figure 10. Northern blot analysis of rat DPP9 RNA.

Figure 11. Detection of DPP9 cDNA in CEM cells.

Figure 12. Detection of murine DPP9 nucleotide sequence.

DETAILED DESCRIPTION OF THE INVENTION

EXAMPLES

General

Restriction enzymes and other enzymes used in cloning were obtained from Boehringer Mannheim Roche. Standard molecular biology techniques were used unless indicated otherwise.

DPP9 Cloning

The nucleotide sequence of DPP8 shown in Figure 1 was used to search the GenBank database for homologous nucleotide sequences. Nucleotide sequences referenced by GenBank accession numbers AC005594 and AC005783 were detected and named GDD. The GDD nucleotide sequence is 39.5 kb and has 19 predicted exons. The analysis of the predicted exon-intron boundaries in GDD suggests that the predicted open reading frame of GDD is 3.6 kb in length.

In view of the homology of DPP8 and the GDD nucleotide sequences, we hypothesised the existence of DPPIV-like molecules other than DPP8. We used oligonucleotide primers derived from the nucleotide sequence of GDD and reverse transcription PCR (RT-PCR) to isolate a cDNA encoding DPPIV-like molecules.

RT-PCR amplification of human liver RNA derived from a pool of 4 patients with autoimmune hepatitis using the primers GDD pr 1F and GDD pr 1R (Table 1) produced a 500 base pair product. This suggested that DPPIV-like molecules are likely to be expressed in liver cells derived from individuals with autoimmune hepatitis and that RNA derived from these cells is likely to be a suitable source for isolating cDNA clones encoding DPPIV-like molecules.

Primers GDD pr 3F and GDD pr 1R (Table 1) were then used to isolate a cDNA clone encoding a DPP4-like molecule. A 1.6 kb fragment was observed named DPP4-like-2a. Primers GDD

pr 15F and GDD pr 7R (Table 1) were then used to isolate a cDNA clone encoding a DPP4-like molecule. A 1.9 kb product was observed and named DPP4-like-2b. As described further herein, the sequence of DPP4-like-2b overlaps with the sequence of DPP4-like-2a.

The DPP4-like-2a and 2b fragments were gel purified using WIZARD® PCR preps kit and cloned into the pGEM®-T-easy plasmid vector using the *Eco*RI restriction sites. The ligation reaction was used to transform JM109 competent cells. The plasmid DNA was prepared by miniprep. The inserts were released by *Eco*RI restriction digestion. The DNA was sequenced in both directions using the M13Forward and M13Reverse sequencing primers. The complete sequence of DPP4-like-2a and 2b fragments was derived by primer walking.

The nucleotide sequence 5′ adjacent to DPP4-like-2b was obtained by 5'RACE using dC tailing and the gene specific primers GDD GSP1.1 and 2.1 (Table 1). A fragment of 500 base pairs (DPP4-like-2c) was observed. The fragment was gel purified using WIZARD® PCR preps kit and cloned into the pGEM®-T-easy plasmid vector using the *Eco*RI restriction sites. The ligation reaction was used to transform JM109 competent cells. The plasmid DNA was prepared by miniprep. The inserts were released by *Eco*RI restriction digestion. The DNA was sequenced in both directions using the M13Forward and M13Reverse sequencing primers.

We identified further sequences, BE727051 and BE244612, with identity to the 5' end of DPP9. These were discovered while performing BLASTn with the 5' end of the DPP9 nucleotide sequence. BE727051 contained further 5' sequence for DPP9, which was also present in the genomic sequence for DPP9 on chromosome 19p13.3. This was used to design primer DPP9-22F (5'GCCGGCGGGTCCCCTGTGTCCG3'). Primer 22F

was used in conjunction with primer GDD3'end (5'GGGCGGGACAAAGTGC CTCACTGG3') on cDNA made from the human CEM cell line to produce a 3000bp product as expected Figure 11.

Nucleotide sequence analysis of DPP4-like-2a, 2b, and 2c fragments.

An analysis of the nucleotide sequence of fragments DPP4-like 2a, 2b and 2c with the Sequencher™ version 3.0 computer program (Figure 3), and the 5′ fragment isolated by primers DPP9-22F and GDD3′end, revealed the nucleotide sequence shown in Figure 4.

The predicted amino acid sequence shown in Figure 4 was compared to a predicted amino acid sequence encoded by a predicted open reading frame of GDD (predicted from the nucleotide sequence referenced by GenBank Accession Nos. AC005594 and AC005783), to determine the relatedness of the nucleotide sequence of Figure 4 to the nucleotide sequence of the predicted open reading frame of GDD (Figure 5). Regions of amino acid identity were observed suggesting that there may be regions of nucleotide sequence identity of the predicted open reading frame of GDD and the sequence of Figure 4. However, as noted in Figure 5, there are regions of amino acid sequence encoded by the sequence of Figure 4 and the amino acid sequence encoded by the predicted open reading frame of GDD which are not identical, demonstrating that the nucleotide sequences encoding the predicted open reading frame of GDD and the sequence shown in Figure 4 are different nucleotide sequences.

As described further herein, the predicted amino acid sequence encoded by the cDNA sequence shown in Figure 4 is homologous to the amino acid sequence of DPP8 (Figure 6). Accordingly, and as a cDNA consisting of the nucleotide

sequence shown in Figure 4 was not known, the sequence shown in Figure 4 was named cDNA DPP9.

The predicted amino acid sequence encoded by cDNA DPP9 (called DPP9) is 969 amino acids and is shown in Figure 4. The alignment of DPP9 and DPP8 amino acid sequences suggests that the nucleotide sequence shown in Figure 4 may be a partial length clone. Notwithstanding this point, as discussed below, the inventors have found that the alignment of DPP9 amino acid sequence with the amino acid sequences of DPP8, DPP4 and FAP shows that DPP9 comprises sequence necessary for providing enzymolysis and utility. In view of the similarity between DPP9 and DPP8, a full length clone may be of the order of 882 amino acids. A full length clone could be obtained by standard techniques, including for example, the RACE technique using an oligonucleotide primer derived from the 5′ end of cDNA DPP9.

In view of the homology between the DPP8 and DPP9 amino acid sequences, it is likely that cDNA DPP9 encodes an amino acid sequence which has dipeptidyl peptidase enzymatic activity. Specifically, it is noted that the DPP9 amino acid sequence contains the catalytic triad Ser-Asp-His in the order of a non-classical serine protease as required for the charge relay system. The serine recognition site characteristic of DPP4 and DPP4-like family members, GYSWGG, surrounds the serine residue also suggesting that DPP9 cDNA will encode a DPP4-like enzyme activity.

Further, DPP9 amino acid sequence also contains the two glutamic acid residues located at positions 205 and 206 in DPPIV. These are believed to be essential for the dipeptidyl peptidase enzymatic activity. By sequence alignment with DPPIV, the residues in DPP8 predicted to

play a pivotal role in the pore opening mechanism in Blade 2 of the propeller are E^{259}, E^{260}. These are equivalent to the residues Glu^{205} and Glu^{206} in DPPIV which previously have been shown to be essential for DPPIV enzyme activity. A point mutation Glu259Lys was made in DPP8 cDNA using the Quick Change Site directed Mutagenesis Kit(Stratagene, La Jolla). COS-7 cells transfected with wildtype DPP8 cDNA stained positive for H-Ala-Pro4MbNA enzyme activity while the mutant cDNA gave no staining. Expression of DPP8 protein was demonstrated in COS cells transfected with wildtype and mutant cDNAs by immunostaining with anti-V5 mAB. This mAB detects the V5 epitope that has been tagged to the C-terminus of DPP8 protein. Point mutations were made to each of the catalytic residues of DPP8, Ser739A, Asp817Ala and His849Ala, and each of these residues were also determined to be essential for DPP8 enzyme activity. In summary, the residues that have been shown experimentally to be required for enzyme activity in DPPIV and DPP8 are present in the DPP9 amino acid sequence: Glu^{354}, Glu^{355}, Ser ^{836}, Asp^{914} and His^{946}.

The DPP9 amino acid sequence shows the closest relatedness to DPP8, having 77% amino acid similarity and 60% amino acid identity. The relatedness to DPPIV is 25% amino acid identity and 47% amino acid similarity. The % similarity was determined by use of the program/algorithm "GAP" which is available from Genetics Computer Group(GCG),Wisconsin.

DPP9 mRNA Expression Studies

DPP4-like-2a was used to probe a Human Master RNA Blot™ (CLONTECH Laboratories Inc., USA) to study DPP9 tissue expression and the relative levels of DPP9 mRNA expression.

The DPP4-like-2a fragment hybridised to all tissue mRNA samples on the blot. The hybridisation also indicated high

levels of DPP9 expression in most of the tissues samples on the blot (data not shown).

The DPP4-like-2a fragment was then used to probe two Multiple Tissue Northern Blots™ (CLONTECH Laboratories Inc., USA) to examine the mRNA expression and to determine the size of DPP9 mRNA transcript.

The autoradiographs of the DPP9 Multiple Tissue Northern blot are shown in Figure 8. The DPP9 transcript was seen in all tissues examined confirming the results obtained from the Master RNA blot. A single major transcript 4.4 kb in size was seen in all tissues represented on two Blots after 16 hours of exposure. Weak bands could also be seen in some tissues after 6 hours of exposure. The DPP9 transcript was smaller than the 5.1 kb mRNA transcript of DPP8. A minor, very weak transcript 4.8 kb in size was also seen in the spleen, pancreas, peripheral blood leukocytes and heart. The highest mRNA expression was observed in the spleen and heart. Of all tissues examined the thymus had the least DPP9 mRNA expression. The Multiple Tissue Northern Blots were also probed with a β -actin positive control. A 2.0 kb band was seen in all tissues. In addition as expected a 1.8 kb β-actin band was seen in heart and skeletal muscle.

<u>Rat DPP9 expression</u>

A Rat Multiple Tissue Northern Blot (CLONTECH Laboratories, Inc., USA;catalogue #: 7764-1) was hybridised with a human DPP9 radioactively labeled probe, made using Megaprime DNA Labeling kit and [32P] dCTP (Amersham International plc, Amersham, UK). The DPP9 PCR product used to make the probe was generated using Met3F (GGCTGAGAG GAT GGCCACCAC CGGG) as the forward primer and GDD 3'end (GGGCGGGACAAAGTGC CTCACTGG) as the reverse primer. The hybridisation was

carried out according to the manufacturers' instructions at 60° C to detect cross-species hybridisation. After overnight hybridization the blot was washed at room temperature (2x SSC, 0.1% SDS) then at 40° C (0.1xSSC, 0.1%SDS).

The human cDNA probe identified two bands in all tissues examined except in testes. A major transcript of 4 kb in size was seen in all tissues except testes. This 4 kb transcript was strongly expressed in the liver, heart and brain. A second weaker transcript 5.5 kb in size was present in all tissues except skeletal muscle and testes. However in the brain the 5.5kb transcript was expressed at a higher level than the 4.4 kb transcript. In the testes only one transcript approximately 3.5 kb in size was detected. Thus, rat DPP9 mRNA hybridised with a human DPP9 probe indicating significant homology between DPP9 of the two species. The larger 5.5 kbtranscript observed may be due to crosshybridisation to rat DPP8.

Mouse DPP9 expression

A Unigene cluster for Mouse DPP9 was identified (UniGene Cluster Mm.33185) by homology to human DPP9. An analysis of expressed sequence tags contained in this cluster and mouse genomic sequence (AC026385) for Chromosome 17 with the Sequencer™ version 3.0 computer program revealed the nucleotide sequence shown in Figure 9. This 3517bp cDNA encodes a 869 aa mouse DPP9 protein (missing N-terminus) with 91% amino acid identity and 94 % amino acid similarity to human DPP9. The mouse DPP9 amino acid sequence also has the residues required for enzyme activity, Ser, Asp and His and the two Glu residues.

The primers mgdd-pr1F (5'ACCTGGGAGGAAGCACCCCACTGTG3') and mgdd-pr4R (5'TTCCACCTGGTCCTCAATCTCC3') were designed from

this sequence and used to amplify a 452 bp product as expected from liver mouse cDNA, as described below.

RNA preparation

B57Bl6 mice underwent carbon tetrachloride treatment to induce liver fibrosis. Liver RNA were prepared from snap-frozen tissues using the TRIzol® Reagent and other standard methods.

cDNA synthesis

2μg of liver RNA was reverse-transcribed using SuperScript II RNase H- Reverse Transcriptase (Gibco BRL).

PCR

PCR using mDPP9- 1F (ACCTGGGAGGAAGCACCCCACTGTG) as the forward primer and mDPP9-2R (CTCTCCACATGCAGGGCTACAGAC) as the reverse primer was used to synthesise a 550 base pair mouse DPP9 fragment. The PCR products were generated using AmpliTaq Gold® DNA Polymerase. The PCR was performed as follows: denaturation at 95° C for 10 min, followed by 35 cycles of denaturation at 95 ° C for 30 seconds, primer annealing at 60 ° C for 30 seconds, and an extension 72° C for 1 min.

Southern Blot

DPP9 PCR products from six mice as well as the largest human DPP9 PCR product were run on a 1% agarose gel. The DNA on the gel was then denatured using 0.4 M NaOH and transferred onto a Hybond-N+ membrane (Amersham International plc, Amersham, UK). The largest human DPP9 PCR product was radiolabeled using the Megaprime DNA Labeling kit and [32^P] dCTP (Amersham International plc, Amersham, UK). Unincorporated label was removed using a NAP column (Pharmacia Biotech, Sweden) and the denatured probe was incubated with the membrane for 2 hours at 60° C in Express Hybridisation solution (CLONTECH Laboratories, Inc., USA). (Figure 12). Thus, DPP9 mRNA of appropriate size was detected in fibrotic mouse liver using rt-PCR. Furthermore, the single band of mouse DPP9 cDNA hybridised

with a human DPP9 probe indicating significant homology between DPP9 of the two species.

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CLAIMS

1. A peptide which comprises:

(a) the sequence shown in SEQ ID NO:2; or

(b) the amino acid sequences: His^{833}GlyTrpSerTyrGlyGlyPheLeu; Leu^{913}AspGluAsnValHisPhePhe; Glu^{944}ArgHisSerIleArg and Phe^{350}ValIleGlnGluGluPhe, and which has the substrate specificity of the sequence shown in SEQ ID NO:2;or

(c) the sequence which has at least 60% identity with the sequence shown in SEQ ID NO:2, and which has the substrate specificity of the sequence shown in SEQ ID NO:2; or

(d) the sequence shown in SEQ ID NO:4.

2. A peptide according to claim 1 (c), wherein the amino acid identity is at least 75%.

3. A peptide according to claim 1 (c) wherein the amino acid identity is at least 95%.

4. A fragment of the sequence shown in SEQ ID NO:2 which has the substrate specificity of the sequence shown in SEQ ID NO:2.

5. A fragment according to claim 4 which comprises part of the sequence shown in SEQ ID NO:2.

6. A fusion protein comprising the amino acid sequence shown in SEQ ID NO:2 linked with a further amino acid sequence, the fusion protein having the substrate specificity of the sequence shown in SEQ ID NO:2.

7. A fusion protein according to claim 6 wherein the further amino acid sequence is selected from the group

consisting of GST, V5 epitope and His tag.

8. A method of identifying a molecule capable of inhibiting cleavage of a substrate by DPP9 comprising the following steps:

(a) contacting DPP9 with the molecule;

(b) contacting DPP9 of step (a) with a substrate capable of being cleaved by DPP9, in conditions sufficient for cleavage of the substrate by DPP9; and

(c) detecting substrate not cleaved by DPP9, to identify that the molecule is capable of inhibiting cleavage of the substrate by DPP9.

9. A method of identifying a molecule capable of inhibiting specifically, the cleavage of a substrate by DPP9, the method comprising the following steps:

(a) contacting DPP9 and a further protease with the molecule;

(b) contacting DPP9 and the further protease of step (a) with a substrate capable of being cleaved by DPP9 and the further protease, in conditions sufficient for cleavage of the substrate by DPP9 and the further protease; and

(c) detecting substrate not cleaved by DPP9, but cleaved by the further protease, to identify that the molecule is capable of inhibiting specifically, the cleavage of the substrate by DPP9.

10. A method of reducing or inhibiting the catalytic activity of DPP9, the method comprising the step of contacting DPP9 with an inhibitor of DPP9 catalytic activity.

11. A method of cleaving a substrate comprising the step of contacting the substrate with DPP9 in conditions sufficient for cleavage of the substrate by DPP9.

12. A nucleic acid molecule which:

(a) encodes the sequence shown in SEQ ID NO:2; or

(b) consists of the sequence shown in SEQ ID NO:1; or

(c) is capable of hybridizing to a nucleic acid molecule consisting of the sequence shown in SEQ ID NO:1 in stringent conditions, and which encodes a peptide which has the substrate specificity of the sequence shown in SEQ ID NO:2; or

(d) consists of the sequence shown in SEQ ID NO:3.

13. A nucleic acid molecule according to claim 12 (c) wherein the molecule is capable of hybridising in high stringent conditions.

14. A nucleic acid molecule according to claim 12 which is capable of hybridising to a gene which is located at band p13.3 on human chromosome 19.

15. A nucleic acid molecule according to claim 12 which does not contain 5′ or 3′ untranslated regions.

16. A fragment of a nucleic acid molecule consisting of the sequence shown in SEQ ID NO:1, which encodes a peptide which has the substrate specificity of the sequence shown in SEQ ID NO:2.

17. A fragment according to claim 16 which consists of part of the sequence shown in SEQ ID NO:1.

18. A vector comprising a nucleic acid molecule according to claim 12.

19. A cell comprising a vector according to claim 18.

20. A composition comprising a peptide according to claim 1.

21. An antibody which is capable of binding to a peptide according to claim 1.

22. An antibody according to claim 21 which is produced by a hybridoma cell.

23. A hybridoma cell capable of making an antibody according to claim 22.

24. A peptide comprising the sequence shown in SEQ ID NO: 7.

25. A nucleic acid molecule comprising the sequence shown in SEQ ID NO:8.

Table 1

FORWARD Primer name	Primer length	Primer sequence (5'- 3')
GDD pr 1f	24mer	GTG GAG ATC GAG GAC CAG GTG GAG
GDD pr 2f	24mer	CAA AGT GAG GAA AAA TGC ACT CCG
GDD pr 2a	24mer	TGA GGA AAA ATG CAC TCC GAG CAG
GDD pr 3f	24mer	AAA CTG GCT GAG TTC CAG ACT GAC
GDD pr 5f	24mer	CGG GGA AGG TGA GCA GAG CCT GAC
GDD pr 6f	24mer	AGA AGC ACC CCA CCG TCC TCT TTG
GDD pr 11f	24mer	GAG AAG GAG CTG GTG CAG CCC TTC
GDD pr 12f	24mer	TCA GAG GGA GAG GAC GAG CTC TGC
GDD pr 14f	24mer	CCG CTT CCA GGT GCA GAA GCA CTC
GDD pr 15f	24mer	CTA CGA CTT CCA CAG CGA GAG TGG
GDD pr 16f	25mer	GAT GAG TCC GAG GTG GAG GTC ATT C

REVERSE Primer name	Primer length	Primer sequence (5'- 3')
GDD pr 1r	24mer	GCT CAG AGG TAT TCC TGT AGA AAG
GDD pr 4r	24mer	CCC ATG TTG GCC AGG CTG GTC TTG
GDD pr 7r	24mer	AGG ACC AGC CAT GGA TGG CAA CTC
GDD pr 8r	24mer	CCG CTC AGC TTG TAG ACG TGC ACG
GDD pr 9r	24mer	TCA TTC TCT GTG CTC GGG ATG AAC
GDD pr 13r	24mer	GCA CAT CCG AGC GCG TGT GGA AAT
GDD pr 17r	24mer	TGG GAG AAG CCG GGC GTG GTG AGG
GDD pr 18r	25mer	GCG GTC GAA CTC TTC CTG TAT GAC G
5'RACE Primer name		
GDD GSP 1.1	18mer	TGA AGG AGA AGA AGG CAG
GDD GSP 2.1	24mer	CCT GAG CAC TGG GTC TTG ATT TCC
5' RACE Abridged Anchor Primer (AAP)	36mer	GGC CAC GCG TCG ATC ATG ACG GGI IGG GII GGG IIG

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   1 CTGCTAAAG CTTCAGG CAAG [illegible] TTCTTAGTG [illegible] TGGGTTGTCACCGGCGCCGCCGCCCACGAAC   100
 101 CCACTCCAACCAGGACCGGAGTGGACCCCCCCCACCATGAAGCCGCCCAGGCCCCCTCCATAGCCGCACGTCGGGACCGTCCCGGCGGGCCGCCGCGAACG   200
 201 AAAATGCAACATGGCAGCAGCAATGGAAACAGAACAGCTGCGGTGTTGAGATATTTGAAACTGCGGACTGTGAGCAGAATATTGAATCACAGCATCGGCCT   300
         M  A  A  A  M  E  T  E  Q  L  C  V  E  I  F  E  T  A  D  C  E  E  N  I  E  S  Q  D  R  P   30
 301 AAATTGGAGCCTTTTTATGTTGAGCGGTATTCCTGGAGTCAGCTTAAAAAGCTGCTTGCCGATACCAGAAAATATCATGGCTACATGATGGCTAAGGCAC   400
  31 K  L  E  P  F  Y  V  E  R  Y  S  W  S  Q  L  K  K  L  L  A  D  T  R  K  Y  H  G  Y  M  M  A  K  A  P   64
 401 CACATGATTTCATGTTTGTGAAGAGGAATGATCCAGATGGACCTCATTCAGACAGAATCTATTACCTTGCCATGTCTGGTGAGAACAGAGAAAATACACT   500
  64  H  D  F  M  F  V  K  R  N  D  P  D  G  P  H  S  D  R  I  Y  Y  L  A  M  S  G  E  N  R  E  N  T  L   97
 501 CTTTTATTCTGAAATTCCCAAAACTATCAATAGAGCAGCAGTCTTAATGCTCTCTTGGAAGCCTCTTTTGGATCTTTTTCAGGCAACACTGGACTATGGA   600
  97  F  Y  S  E  I  P  K  T  I  N  R  A  A  V  L  M  L  S  W  K  P  L  L  D  L  F  Q  A  T  L  D  Y  G   130
 601 ATGTATTCTCGAGAAGAAGAACTATTAAGAGAAAGAAACCGCATTGAACCAGTCGGAATTGCTTCTTACGATTATCCCCAAGGAAGTGGAACATTTCTGT   700
 131 M  Y  S  R  E  E  E  L  L  R  E  R  N  R  I  E  P  V  G  I  A  S  Y  D  Y  P  Q  G  S  G  T  F  L  F   164
 701 TTCAAGCCGGTAGTGGAATTTATCACGTAAAAGATGAAGGCCCACAAGGATTTACGCAACAACCTTTAAGGCCCAATCTAGTGGAAACTAGTTGTCCCAA   800
 164  Q  A  G  S  G  I  Y  H  V  K  D  E  G  P  Q  G  F  T  Q  Q  P  L  R  P  N  L  V  E  T  S  C  P  N   197
 801 CATACGGATGGATCCAAAATTATGCCCCGCTGATCCAGACTGGATTGCTTTTATACATAGCAACGATATTTGGATATCTAACATCGTAACCAGAGAAGAA   900
 197  I  R  M  D  P  K  L  C  P  A  D  P  D  W  I  A  F  I  H  S  N  D  I  W  I  S  N  I  V  T  R  E  E   230
 901 AGGAGACTCACTTATGTGCACAATGAGCTAGCCAACATGGAAGAAGATGCCAGATCAGCTGGAGTCGCTACCTTTGTTCTCCAAGAAGAATTTGATAGAT   1000
 231 R  R  L  T  Y  V  H  N  E  L  A  N  M  E  E  D  A  R  S  A  G  V  A  T  F  V  L  Q  E  E  F  D  R  Y   264
1001 ATTCTGGCTATTGGTGGTGTCCAAAAGCTGAAACAACTCCCAGTGGTGGTAAAATTCTTAGAATTCTATATGAAGAAAATGATGAATCTGAGGTGGAAAT   1100
 264  S  G  Y  W  W  C  P  K  A  E  T  T  P  S  G  G  K  I  L  R  I  L  Y  E  E  N  D  E  S  E  V  E  I   297
1101 TATTCATGTTACATCCCCTATGTTGGAAACAAGGAGGGCAGATTCATTCCGTTATCCTAAAACAGGTACAGCAAATCCTAAAGTCACTTTTAAGATGTCA   1200
 297  I  H  V  T  S  P  M  L  E  T  R  R  A  D  S  F  R  Y  P  K  T  G  T  A  N  P  K  V  T  F  K  M  S   330
1201 GAAATAATGATTGATGCTGAAGGAAGGATCATAGATGTCATAGATAAGGAACTAATTCAACCTTTTGAGATTCTATTTGAAGGAGTTGAATATATTGCCA   1300
 331 E  I  M  I  D  A  E  G  R  I  I  D  V  I  D  K  E  L  I  Q  P  F  E  I  L  F  E  G  V  E  Y  I  A  R   364
1301 GAGCTGGATGGACTCCTGAGGGAAAATATGCTTGGTCCATCCTACTAGATCGCTCCCAGACTCGCCTACAGATAGTGTTGATCTCACCTGAATTATTTAT   1400
 364  A  G  W  T  P  E  G  K  Y  A  W  S  I  L  L  D  R  S  Q  T  R  L  Q  I  V  L  I  S  P  E  L  F  I   397
1401 CCCAGTAGAAGATGATGTTATGGAAAGGCAGAGACTCATTGAGTCAGTGCCTGATTCTGTGACGCCACTAATTATCTATGAAGAAACAACAGACATCTGG   1500
 397  P  V  E  D  D  V  M  E  R  Q  R  L  I  E  S  V  P  D  S  V  T  P  L  I  I  Y  E  E  T  T  D  I  W   430
1501 ATAAATATCCATGACATCTTTCATGTTTTTCCCCAAAGTCACGAAGAGGAAATTGAGTTTATTTTTGCCTCTGAATGCAAAACAGGTTTCCGTCATTTAT   1600
 431 I  N  I  H  D  I  F  H  V  F  P  Q  S  H  E  E  E  I  E  F  I  F  A  S  E  C  K  T  G  F  R  H  L  Y   464
1601 ACAAAATTACATCTATTTTAAAGGAAAGCAAATATAAACGATCCAGTGGTGGGCTGCCTGCTCCAAGTGATTTCAAGTGTCCTATCAAAGAGGAGATAGC   1700
 464  K  I  T  S  I  L  K  E  S  K  Y  K  R  S  S  G  G  L  P  A  P  S  D  F  K  C  P  I  K  E  E  I  A   497
1701 AATTACCAGTGGTGAATGGGAAGTTCTTGGCCGGCATGGATCTAATATCCAAGTTGATGAAGTCAGAAGGCTGGTATATTTTGAAGGCACCAAAGACTCC   1800
 497  I  T  S  G  E  W  E  V  L  G  R  H  G  S  N  I  Q  V  D  E  V  R  R  L  V  Y  F  E  G  T  K  D  S   530
1801 CCTTTAGAGCATCACCTGTACGTAGTCAGTTACGTAAATCCTGGAGAGGTGACAAGGCTGACTGACCGTGGCTACTCACATTCTTGCTGCATCAGTCAGC   1900
 531 P  L  E  H  H  L  Y  V  V  S  Y  V  N  P  G  E  V  T  R  L  T  D  R  G  Y  S  H  S  C  C  I  S  Q  H   564
1901 ACTGTGACTTCTTTATAAGTAAGTATAGTAACCAGAAGAATCCACACTGTGTGTCCCTTTACAAGCTATCAAGTCCTGAAGATGACCCAACTTGCAAAAC   2000
 564  C  D  F  F  I  S  K  Y  S  N  Q  K  N  P  H  C  V  S  L  Y  K  L  S  S  P  E  D  D  P  T  C  K  T   597
2001 AAAGGAATTTTGGGCCACCATTTTGGATTCAGCAGGTCCTCTTCCTGACTATACTCCTCCAGAAATTTTCTCTTTTGAAAGTACTACTGGATTTACATTG   2100
 597 K  E  F  W  A  T  I  L  D  S  A  G  P  L  P  D  Y  T  P  P  E  I  F  S  F  E  S  T  T  G  F  T  L   630
2101 TATGGGATGCTCTACAAGCCTCATGATCTACAGCCTGGAAAGAAATATCCTACTGTGCTGTTCATATATGGTGGTCCTCAGGTGCAGTTGGTGAATAATC   2200
 631 Y  G  M  L  Y  K  P  H  D  L  Q  P  G  K  K  Y  P  T  V  L  F  I  Y  G  G  P  Q  V  Q  L  V  N  N  R   664
2201 GGTTTAAAGGAGTCAAGTATTTCCGCTTGAATACCCTAGCCTCTCTAGGTTATGTGGTTGTAGTGATAGACAACAGGGGATCCTGTCACCGAGGGCTTAA   2300
 664  F  K  G  V  K  Y  F  R  L  N  T  L  A  S  L  G  Y  V  V  V  V  I  D  N  R  G  S  C  H  R  G  L  K   697
2301 ATTTGAAGGCGCCTTTAAATATAAAATGGGTCAAATAGAAATTGACGATCAGGTGGAAGGACTCCAATATCTAGCTTCTCGATATGATTTCATTGACTTA   2400
 697  F  E  G  A  F  K  Y  K  M  G  Q  I  E  I  D  D  Q  V  E  G  L  Q  Y  L  A  S  R  Y  D  F  I  D  L   730
2401 GATCGTGTGGGCATCCACGGCTGGTCCTATGGAGGATACCTCTCCCTGATGGCATTAATGCAGAGGTCAGATATCTTCAGGGTTGCTATTGCTGGGGCCC   2500
 731 D  R  V  G  I  H  G  W  S  Y  G  G  Y  L  S  L  M  A  L  M  Q  R  S  D  I  F  R  V  A  I  A  G  A  P   764
2501 CAGTCACTCTGTGGATCTTCTATGATACAGGATACACGGAACGTTATATGGGTCACCCTGACCAGAATGAACAGGGCTATTACTTAGGATCTGTGGCCAT   2600
 764  V  T  L  W  I  F  Y  D  T  G  Y  T  E  R  Y  M  G  H  P  D  Q  N  E  Q  G  Y  Y  L  G  S  V  A  M   797
2601 GCAAGCAGAAAAGTTCCCCTCTGAACCAAATCGTTTACTGCTCTTACATGGTTTCCTGGATGAGAATGTCCATTTTGCACATACCAGTATATTACTGAGT   2700
 797  Q  A  E  K  F  P  S  E  P  N  R  L  L  L  L  H  G  F  L  D  E  N  V  H  F  A  H  T  S  I  L  L  S   830
2701 TTTTTAGTGAGGGCTGGAAAGCCATATGATTTACAGATCTATCCTCAGGAGAGACACAGCATAAGAGTTCCTGAATCGGGAGAACATTATGAACTGCATC   2800
 831 F  L  V  R  A  G  K  P  Y  D  L  Q  I  Y  P  Q  E  R  H  S  I  R  V  P  E  S  G  E  H  Y  E  L  H  L   864
2801 TTTTGCACTACCTTCAAGAAAACCTTGGATCACGTATTGCTGCTCTAAAAGTGATATAATTTTGACCTGTGTAGAACTCTCTGGTATACACTGGCTATTT   2900
 864  L  H  Y  L  Q  E  N  L  G  S  R  I  A  A  L  K  V  I  *                                            897
2901 AACCAAATCACCAGGTTTAATCAACAGAAAACACAGAATTGATCATCACATTTTGATACCTGCCATCTAACATCTACTCCTGAAAATAAATGTGGTCCCA   3000
3001 TGCAGGGGTCTACGGTTTGTGGTACTAATCTAATACCTTAACCCCACATGCTCAAAATCAAATGATACATATTCCTGAGAGACCCACCAATACCATAACA   3100
3101 ATTACTAAAAAAAAAAAAAAA   3121
```

Figure 1

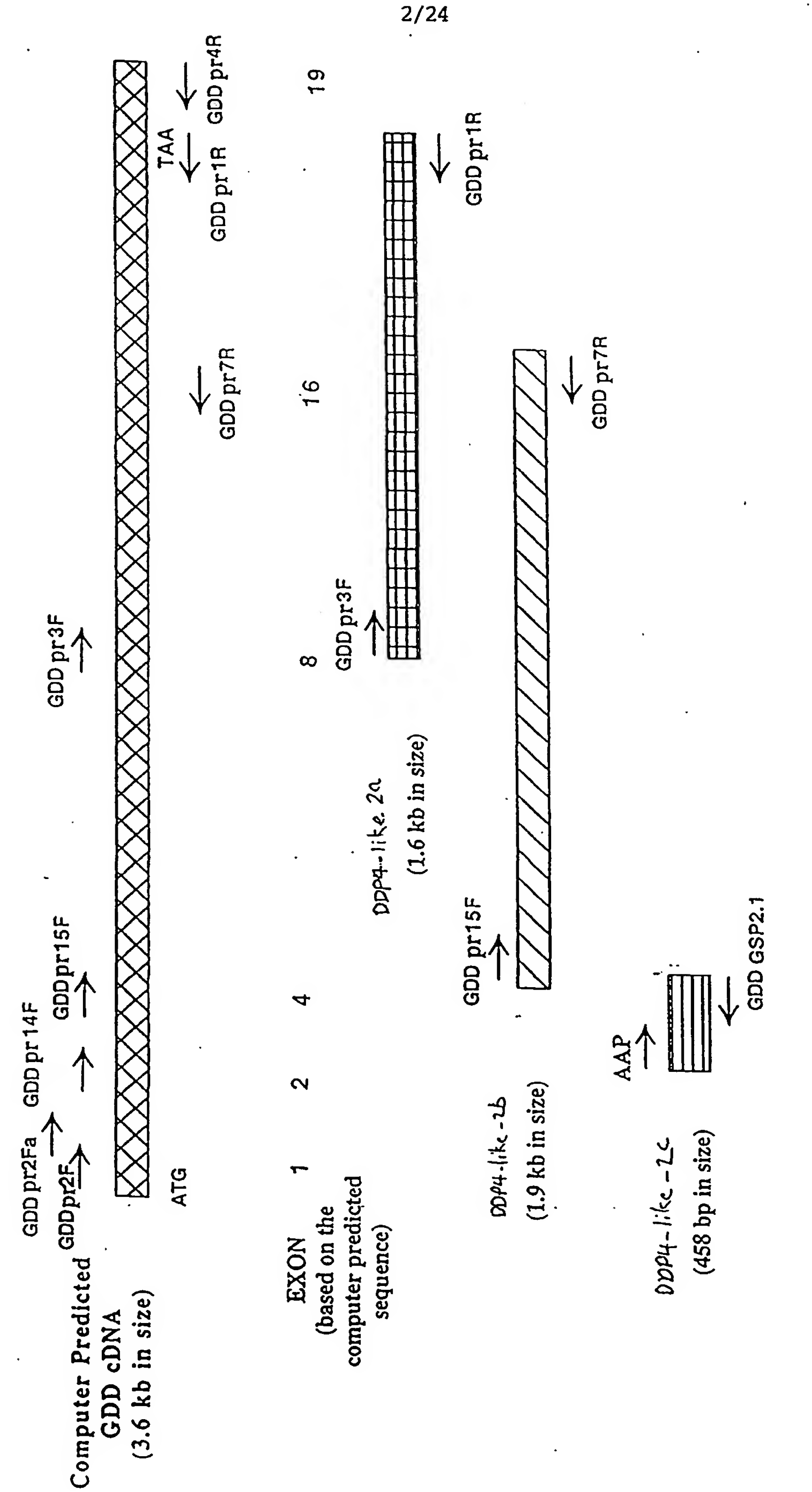
Computer Predicted GDD cDNA (3.6 kb in size)
GDD pr2Fa
GDD pr2F
GDD pr14F
GDD pr15F
GDD pr3F
GDD pr7R
GDD pr1R
TAA
GDD pr4R
ATG
EXON (based on the computer predicted sequence)
1
2
4
8
16
19
DDP4-like 2a (1.6 kb in size)
GDD pr3F
GDD pr1R
DDP4-like -2b (1.9 kb in size)
GDD pr15F
GDD pr7R
DDP4-like -2c (458 bp in size)
AAP
GDD GSP2.1

Figure 2

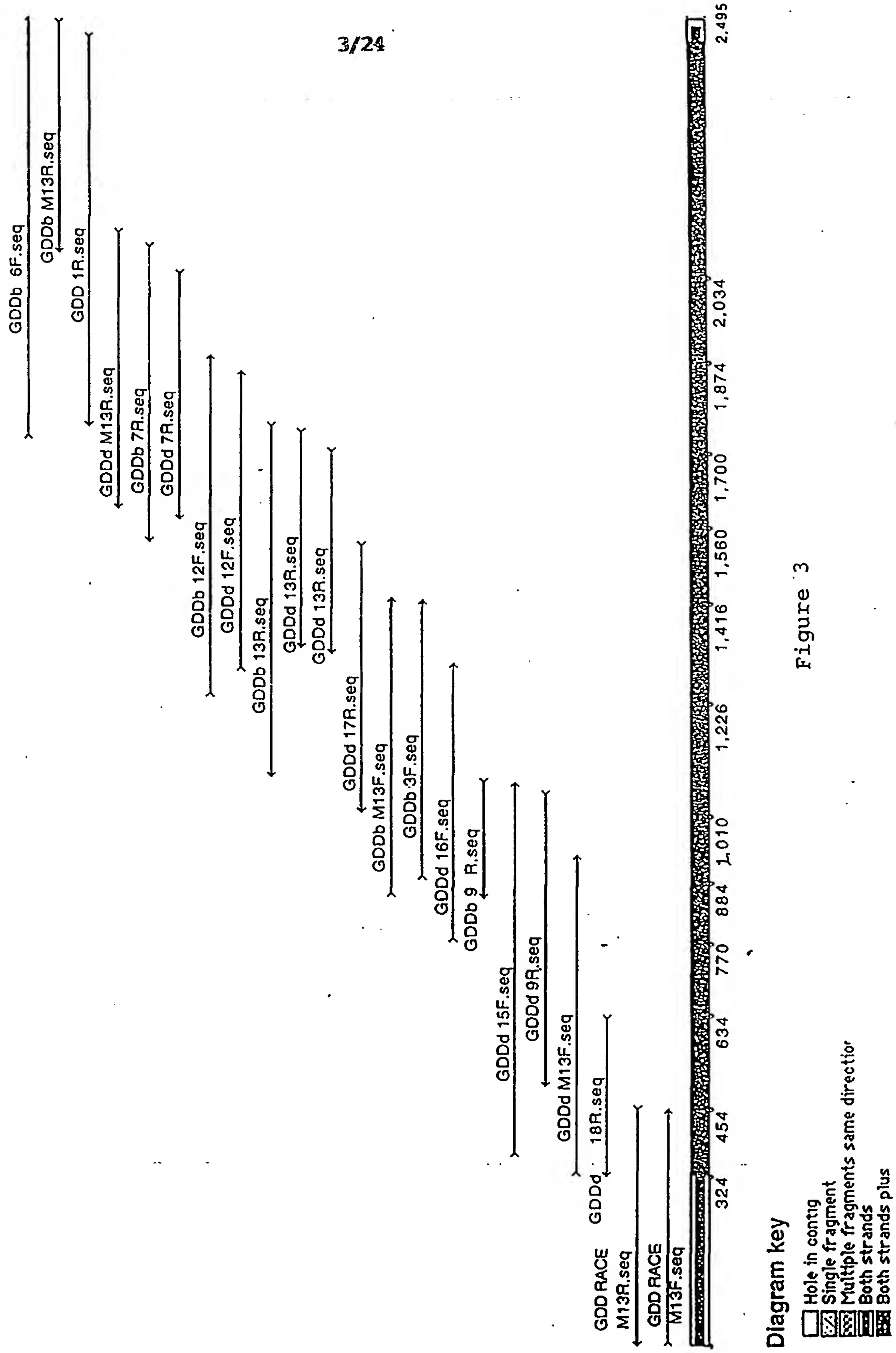
GDDb 6F.seq
GDDb M13R.seq
GDD 1R.seq
GDDd M13R.seq
GDDb 7R.seq
GDDd 7R.seq
GDDb 12F.seq
GDDd 12F.seq
GDDb 13R.seq
GDDd 13R.seq
GDDd 13R.seq
GDDd 17R.seq
GDDb M13F.seq
GDDb 3F.seq
GDDd 16F.seq
GDDb 9 R.seq
GDDd 15F.seq
GDDd 9R.seq
GDDd M13F.seq
GDDd 18R.seq
GDD RACE M13R.seq
GDD RACE M13F.seq
324
454
634
770
884
1,010
1,226
1,416
1,560
1,700
1,874
2,034
2,495
Diagram key
Hole in contig
Single fragment
Multiple fragments same direction
Both strands
Both strands plus

Figure 3

```
                10                            30                            50
  1   CGGCGGGTCCCCTGTGTCCGCCGCGGCTGTCGTCCCCCGCTCCCGCCACTTCCGGGGTCG    60
  1   R  R  V  P  C  V  R  R  G  C  R  P  P  L  P  P  L  P  G  S      20

                70                            90                           110
 61   CAGTCCCGGGCATGGAGCCGCGACCGTGAGGCGCCGCTGGACCCGGGACGACCTGCCCAG   120
 21   Q  S  R  A  W  S  R  D  R  E  A  P  L  D  P  G  R  P  A  Q      40

               130                           150                           170
121   TCCGGCCGCCGCCCCACGTCCCGGTCTGTGTCCCACGCCTGCAGCTGGAATGGAGGCTCT   180
 41   S  G  R  R  P  T  S  R  S  V  S  H  A  C  S  W  N  G  G  S      60

               190                           210                           230
181   CTGGACCCTTTAGAAGGCACCCCTGCCCTCCTGAGGTCAGCTGAGCGGTTAATGCGGAAG   240
 61   L  D  P  L  E  G  T  P  A  L  L  R  S  A  E  R  L  M  R  K      80

               250                           270                           290
241   GTTAAGAAACTGCGCCTGGACAAGGAGAACACCGGAAGTTGGAGAAGCTTCTCGCTGAAT   300
 81   V  K  K  L  R  L  D  K  E  N  T  G  S  W  R  S  F  S  L  N     100

               310                           330                           350
301   TCCGAGGGGGCTGAGAGGATGGCCACCACCGGGACCCCAACGGCCGACCGAGGCGACGCA   360
101   S  E  G  A  E  R  M  A  T  T  G  T  P  T  A  D  R  G  D  A     120

               370                           390                           410
361   GCCGCCACAGATGACCCGGCCGCCCGCTTCCAGGTGCAGAAGCACTCGTGGGACGGGCTC   420
121   A  A  T  D  D  P  A  A  R  F  Q  V  Q  K  H  S  W  D  G  L     140

               430                           450                           470
421   CGGAGCATCATCCACGGCAGCCGCAAGTACTCGGGCCTCATTGTCAACAAGGCGCCCCAC   480
141   R  S  I  I  H  G  S  R  K  Y  S  G  L  I  V  N  K  A  P  H     160

               490                           510                           530
481   GACTTCCAGTTTGTGCAGAAGACGGATGAGTCTGGGCCCCACTCCCACCGCCTCTACTAC   540
161   D  F  Q  F  V  Q  K  T  D  E  S  G  P  H  S  H  R  L  Y  Y     180

               550                           570                           590
541   CTGGGAATGCCATATGGCAGCCGGGAGAACTCCCTCCTCTACTCTGAGATTCCCAAGAAG   600
181   L  G  M  P  Y  G  S  R  E  N  S  L  L  Y  S  E  L  P  K  K     200

               610                           630                           650
601   GTCCGGAAAGAGGCTCTGCTGCTCCTGTCCTGGAAGCAGATGCTGGATCATTTCCAGGCC   660
201   V  R  K  E  A  L  L  L  L  S  W  K  Q  M  L  D  H  F  Q  A     220

               670                           690                           710
661   ACGCCCCACCATGGGGTCTACTCTCGGGAGGAGGAGCTGCTGAGGGAGCGGAAACGCCTG   720
221   T  P  H  H  G  V  Y  S  R  E  E  E  L  L  R  E  R  K  R  L     240

               730                           750                           770
721   GGGGTCTTCGGCATCACCTCCTACGACTTCCACAGCGAGAGTGGCCTCTTCCTCTTCCAG   780
241   G  V  F  G  I  T  S  Y  D  F  H  S  E  S  G  L  F  L  F  Q     260

               790                           810                           830
781   GCCAGCAACAGCCTCTTCCACTGCCGCGACGGCGGCAAGAACGGCTTCATGGTGTCCCCT   840
261   A  S  N  S  L  F  H  C  R  D  G  G  K  N  G  F  M  V  S  P     280

               850                           870                           890
841   ATGAAACCGCTGGAAATCAAGACCCAGTGCTCAGGGCCCCGGATGGACCCCAAAATCTGC   900
281   M  K  P  L  E  I  K  T  Q  C  S  G  P  R  M  D  P  K  I  C     300
```

FIGURE 4

910 930 950
901 CCTGCCGACCCTGCCTTCTTCTCCTTCAACAATAACAGCGACCTGTGGGTGGCCAACATC 960
301 P A D P A F F S F N N N S D L W V A N I 320

970 990 1010
961 GAGACAGGCGAGGAGCGGCGGCTGACCTTCTGCCACCAAGGTTTATCCAATGTCCTGGAT 1020
321 E T G E E R R L T F C H Q G L S N V L D 340

1030 1050 1070
1021 GACCCCAAGTCTGCGGGTGTGGCCACCTTCGTCATACAGGAAGAGTTCGACCGCTTCACT 1080
341 D P K S A G V A T F V I Q E E F D R F T 360

1090 1110 1130
1081 GGGTACTGGTGGTGCCCCACAGCCTCCTGGGAAGGTTCAGAGGGCCTCAAGACGCTGCGA 1140
361 G Y W W C P T A S W E G S E G L K T L R 380

1150 1170 1190
1141 ATCCTGTATGAGGAAGTCGATGAGTCCGAGGTGGAGGTCATTCACGTCCCCTCTCCTGCG 1200
381 I L Y E E V D E S E V E V I H V P S P A 400

1210 1230 1250
1201 CTAGAAGAAAGGAAGACGGACTCGTATCGGTACCCCAGGACAGGCAGCAAGAATCCCAAG 1260
401 L E E R K T D S Y R Y P R T G S K N P K 420

1270 1290 1310
1261 ATTGCCTTGAAACTGGCTGAGTTCCAGACTGACAGCCAGGGCAAGATCGTCTCGACCCAG 1320
421 I A L K L A E F Q T D S Q G K I V S T Q 440

1330 1350 1370
1321 GAGAAGGAGCTGGTGCAGCCCTTCAGCTCGCTGTTCCCGAAGGTGGAGTACATCGCCAGG 1380
441 E K E L V Q P F S S L F P K V E Y I A R 460

1390 1410 1430
1381 GCCGGGTGGACCCGGGATGGCAAATACGCCTGGGCCATGTTCCTGGACCGGCCCCAGCAG 1440
461 A G W T R D G K Y A W A M F L D R P Q Q 480

1450 1470 1490
1441 TGGCTCCAGCTCGTCCTCCTCCCCCCGGCCCTGTTCATCCCGAGCACAGAGAATGAGGAG 1500
481 W L Q L V L L P P A L F I P S T E N E E 500

1510 1530 1550
1501 CAGCGGCTAGCCTCTGCCAGAGCTGTCCCCAGGAATGTCCAGCCGTATGTGGTGTACGAG 1560
501 Q R L A S A R A V P R N V Q P Y V V Y E 520

1570 1590 1610
1561 GAGGTCACCAACGTCTGGATCAATGTTCATGACATCTTCTATCCCTTCCCCCAATCAGAG 1620
521 E V T N V W I N V H D I F Y P F P Q S E 540

1630 1650 1670
1621 GGAGAGGACGAGCTCTGCTTTCTCCGCGCCAATGAATGCAAGACCGGCTTCTGCCATTTG 1680
541 G E D E L C F L R A N E C K T G F C H L 560

1690 1710 1730
1681 TACAAAGTCACCGCCGTTTTAAAATCCCAGGGCTACGATTGGAGTGAGCCCTTCAGCCCC 1740
561 Y K V T A V L K S Q G Y D W S E P F S P 580

1750 1770 1790
1741 GGGGAAGATGAATTTAAGTGCCCCATTAAGGAAGAGATTGCTCTGACCAGCGGTGAATGG 1800
581 G E D E F K C P I K E E I A L T S G E W 600

FIGURE 4

```
          1810                          1830                          1850
1801 GAGGTTTTGGCGAGGCACGGCTCCAAGATCTGGGTCAATGAGGAGACCAAGCTGGTGTAC 1860
601  E  V  L  A  R  H  G  S  K  I  W  V  N  E  E  T  K  L  V  Y  620

          1870                          1890                          1910
1861 TTCCAGGGCACCAAGGACACGCCGCTGGAGCACCACCTCTACGTGGTCAGCTATGAGGCG 1920
621  F  Q  G  T  K  D  T  P  L  E  H  H  L  Y  V  V  S  Y  E  A  640

          1930                          1950                          1970
1921 GCCGGCGAGATCGTACGCCTCACCACGCCCGGCTTCTCCCATAGCTGCTCCATGAGCCAG 1980
641  A  G  E  I  V  R  L  T  T  P  G  F  S  H  S  C  S  M  S  Q  660

          1990                          2010                          2030
1981 AACTTCGACATGTTCGTCAGCCACTACAGCAGCGTGAGCACGCCGCCCTGCGTGCACGTC 2040
661  N  F  D  M  F  V  S  H  Y  S  S  V  S  T  P  P  C  V  H  V  680

          2050                          2070                          2090
2041 TACAAGCTGAGCGGCCCCGACGACGACCCCCTGCACAAGCAGCCCCGCTTCTGGGCTAGC 2100
681  Y  K  L  S  G  P  D  D  D  P  L  H  K  Q  P  R  F  W  A  S  700

          2110                          2130                          2150
2101 ATGATGGAGGCAGCCAGCTGCCCCCCGGATTATGTTCCTCCAGAGATCTTCCATTTCCAC 2160
701  M  M  E  A  A  S  C  P  P  D  Y  V  P  P  E  I  F  H  F  H  720

          2170                          2190                          2210
2161 ACGCGCTCGGATGTGCGGCTCTACGGCATGATCTACAAGCCCCACGCCTTGCAGCCAGGG 2220
721  T  R  S  D  V  R  L  Y  G  M  I  Y  K  P  H  A  L  Q  P  G  740

          2230                          2250                          2270
2221 AAGAAGCACCCCACCGTCCTCTTTGTATATGGAGGCCCCCAGGTGCAGCTGGTGAATAAC 2280
741  K  K  H  P  T  V  L  F  V  Y  G  G  P  Q  V  Q  L  V  N  N  760

          2290                          2310                          2330
2281 TCCTTCAAAGGCATCAAGTACTTGCGGCTCAACACACTGGCCTCCCTGGGCTACGCCGTG 2340
761  S  F  K  G  I  K  Y  L  R  L  N  T  L  A  S  L  G  Y  A  V  780

          2350                          2370                          2390
2341 GTTGTGATTGACGGCAGGGGCTCCTGTCAGCGAGGGCTTCGGTTCGAAGGGGCCCTGAAA 2400
781  V  V  I  D  G  R  G  S  C  Q  R  G  L  R  F  E  G  A  L  K  800

          2410                          2430                          2450
2401 AACCAAATGGGCCAGGTGGAGATCGAGGACCAGGTGGAGGGCCTGCAGTTCGTGGCCGAG 2460
801  N  Q  M  G  Q  V  E  I  E  D  Q  V  E  G  L  Q  F  V  A  E  820

          2470                          2490                          2510
2461 AAGTATGGCTTCATCGACCTGAGCCGAGTTGCCATCCATGGCTGGTCCTACGGGGGCTTC 2520
821  K  Y  G  F  I  D  L  S  R  V  A  I  H  G  W  S  Y  G  G  F  840

          2530                          2550                          2570
2521 CTCTCGCTCATGGGGCTAATCCACAAGCCCCAGGTGTTCAAGGTGGCCATCGCGGGTGCC 2580
841  L  S  L  M  G  L  I  H  K  P  Q  V  F  K  V  A  I  A  G  A  860

          2590                          2610                          2630
2581 CCGGTCACCGTCTGGATGGCCTACGACACAGGGTACACTGAGCGCTACATGGACGTCCCT 2640
861  P  V  T  V  W  M  A  Y  D  T  G  Y  T  E  R  Y  M  D  V  P  880

          2650                          2670                          2690
2641 GAGAACAACCAGCACGGCTATGAGGCGGGTTCCGTGGCCCTGCACGTGGAGAAGCTGCCC 2700
881  E  N  N  Q  H  G  Y  E  A  G  S  V  A  L  H  V  E  K  L  P  900

          2710                          2730                          2750
```

FIGURE 4

```
2701  AATGAGCCCAACCGCTTGCTTATCCTCCACGGCTTCCTGGACGAAAACGTGCACTTTTTC  2760
901   N  E  P  N  R  L  L  I  L  H  G  F  L  D  E  N  V  H  F  F    920

               2770                2790                2810
2761  CACACAAACTTCCTCGTCTCCCAACTGATCCGAGCAGGGAAACCTTACCAGCTCCAGATC  2820
921   H  T  N  F  L  V  S  Q  L  I  R  A  G  K  P  Y  Q  L  Q  I    940

               2830                2850                2870
2821  TACCCCAACGAGAGACACAGTATTCGCTGCCCCGAGTCGGGCGAGCACTATGAAGTCACG  2880
941   Y  P  N  E  R  H  S  I  R  C  P  E  S  G  E  H  Y  E  V  T    960

               2890                2910                2930
2881  TTACTGCACTTTCTACAGGAATACCTCTGAGCCTGCCCACCGGGAGCCGCCACATCACAG  2940
961   L  L  H  F  L  Q  E  Y  L  *

               2950                2970                2990
2941  CACAAGTGGCTGCAGCCTCCGCGGGGAACCAGGCGGGAGGGACTGAGTGGCCCGCGGGCC  3000


3001 CCAGTGAGGCACTTTGTCCCGCCC    3020
```

FIGURE 4

```
101 SWDGLRSIIHGSRKYSGLIVNKAPHDFQFVQKTDESGPHSHRLYYLGHPY 150
        ||||||||||||||||||||||||||||||||||||||||||||||
  1 ....LRSIIHGSRKYSGLIVNKAPHDFQFVQKTDESGPHSHRLYYLGHPY 46

151 GSRENSLLYSEIPKKVRKEALLLLSWKQHLDHFQATPHHGVYSREEELLR 200
    ||||||||||||||||||||||||||||||||||||||||||||||||||
 47 GSRENSLLYSEIPKKVRKEALLLLSWKQHLDHFQATPHHGVYSREEELLR 96

201 ERKRLGVFGITSYDFHSESGLFLFQASNSLFHCRDGGKNGFHVSPGPGCV 250
    ||||||||||||||||||:|||||||||||||||||||||||       |
 97 ERKRLGVFGITSYDFHSEGGLFLFQASNSLFHCRDGGKNGFH.......V 139

251 SPHKPLEIKTQCSGPRHDPKICPADPAFFSFINNSDLWVANIETGEERRL 300
    ||||||||||||||||||||||||||||||||||||||||||||||||||
140 SPHKPLEIKTQCSGPRHDPKICPADPAFFSFINNSDLWVANIETGEERRL 189

301 TFCHQGLSNVLDDPKSAGVATFVIQEEFDRFTGYWWCPTASWE..EGLKT 348
    |||||||||||||||||||||||||||||||||||||||||||  |||||
190 TFCHQGLSNVLDDPKSAGVATFVIQEEFDRFTGYWWCPTASWEGSEGLKT 239

349 LRILYEEVDESEVEVIHVPSPALEERKTDSYRYPRTGSKNPKIALKLAEF 398
    ||||||||||||||||||||||||||||||||||||||||||||||||||
240 LRILYEEVDESEVEVIHVPSPALEERKTDSYRYPRTGSKNPKIALKLAEF 289

399 QTDSQGKIVSTQEKELVQPFSSLFPKVEYIARAG.......AWAMFLDRP 441
    ||||||||||||||||||||||||||||||||||       |||||||||
290 QTDSQGKIVSTQEKELVQPFSSLFPKVEYIARAGWTRDGKYAWAMFLDRP 339

442 QQWLQLVLLPPALFIPSTENEEQRLASARAVPRNVQPYVVYEEVTNVWIN 491
    ||||||||||||||||||||||||||||||||||||||||||||||||||
340 QQWLQLVLLPPALFIPSTENEEQRLASARAVPRNVQPYVVYEEVTNVWIN 389

492 VHDIFYPFPQSEGEDELCFLRANECKTGFCHLYKVTAVLKSQGYDWSEPF 541
    ||||||||||||||||||||||||||||||||||||||||||||||||||
390 VHDIFYPFPQSEGEDELCFLRANECKTGFCHLYKVTAVLKSQGYDWSEPF 439

542 SPGEG........EQSLTNA...........IWVNEETKLVYFQGTKDTP 572
    ||||:        | .||.:           |||||||||||||||||||
440 SPGEDEFKCPIKEEIALTSGEWEVLARHGSKIWVNEETKLVYFQGTKDTP 489

573 LEHHLYVVSYEAAGEIVRLTTPGFSHSCSHSQNFDHFVSHYSSVSTPPCV 622
    ||||||||||||||||||||||||||||||||||||||||||||||||||
490 LEHHLYVVSYEAAGEIVRLTTPGFSHSCSHSQNFDHFVSHYSSVSTPPCV 539

623 HVYKLSGPDDDPLHKQPRFWASHMEAA.........KIFHFHTRSDVRLY 663
    |||||||||||||||||||||||||||          |||||||||||||
540 HVYKLSGPDDDPLHKQPRFWASHMEAASCPPDYVPPEIFHFHTRSDVRLY 589

664 GHIYKPHALQPGKKHPTVLFVYGGPQVQLVNNSFKGIKYLRLNTLASLGY 713
    ||||||||||||||||||||||||||||||||||||||||||||||||||
590 GHIYKPHALQPGKKHPTVLFVYGGPQVQLVNNSFKGIKYLRLNTLASLGY 639

714 AVVVIDGRGSCQRGLRFEGALKNQHGQVEIEDQVEGLQFVAEKYGFIDLS 763
    ||||||||||||||||||||||||||||||||||||||||||||||||||
640 AVVVIDGRGSCQRGLRFEGALKNQHGQVEIEDQVEGLQFVAEKYGFIDLS 689

764 RVAIHGWSYGGFLSLHGLIHKPQVFKVAIAGAPVTVWHAYDTGYTERYHD 813
    ||||||||||||||||||||||||||||||||||||||||||||||||||
690 RVAIHGWSYGGFLSLHGLIHKPQVFKVAIAGAPVTVWHAYDTGYTERYHD 739

814 VPENNQHGYEAGSVALHVEKLPNEPNRLLILHGFLDENVHFFHTNFLVSQ 863
    ||||||||||||||||||||||||||||||||||||||||||||||||||
740 VPENNQHGYEAGSVALHVEKLPNEPNRLLILHGFLDENVHFFHTNFLVSQ 789

864 LIRAGKPYQLQVALPPVSPQIYPNERHSIRCPESGEHYEVTLLHFLQEYL 913
    ||||||||||         |||||||||||||||||||||||||||||||
790 LIRAGKPYQL.........QIYPNERHSIRCPESGEHYEVTLLHFLQEYL 830
```

Figure 5

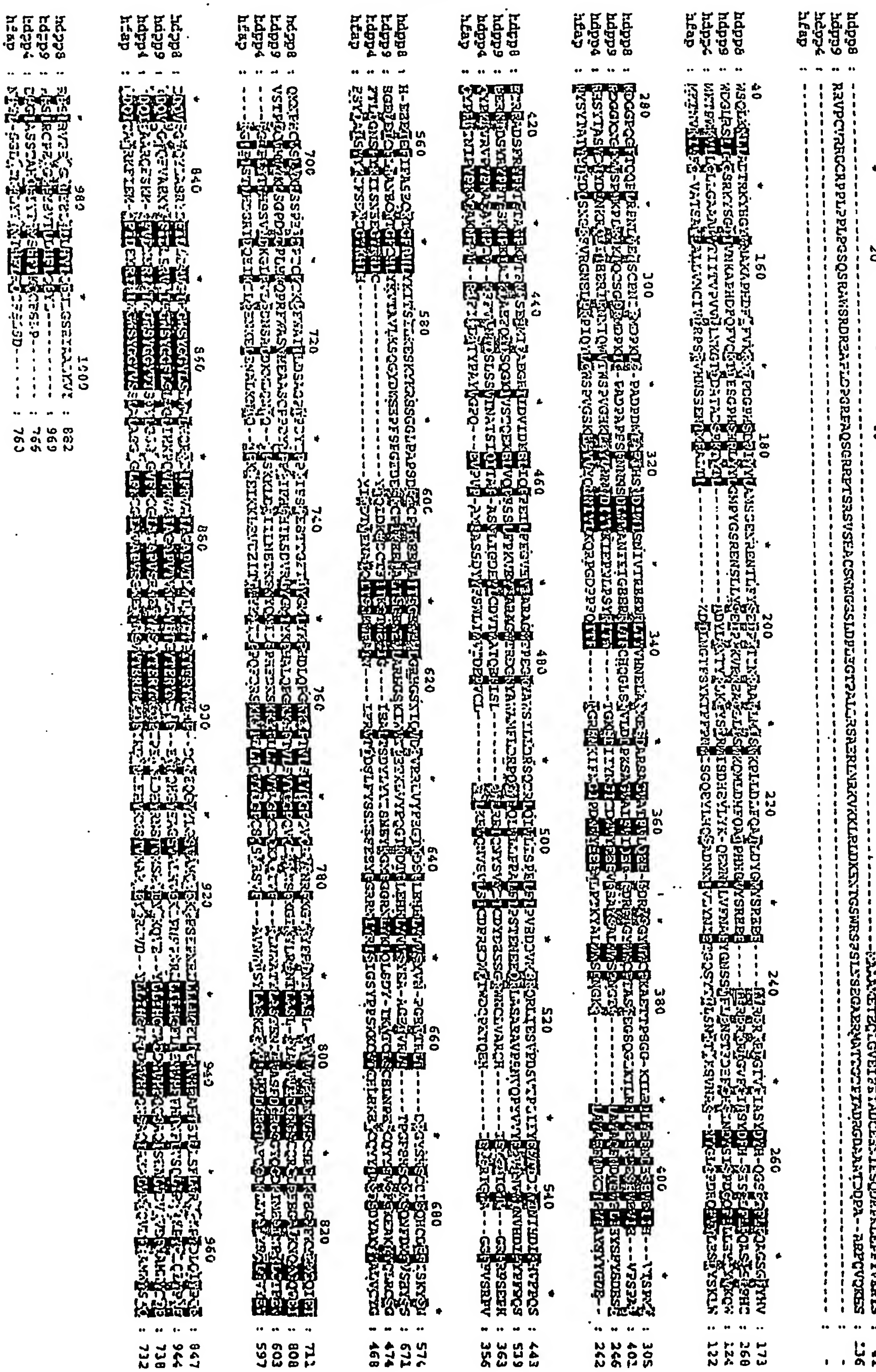

FIGURE 6

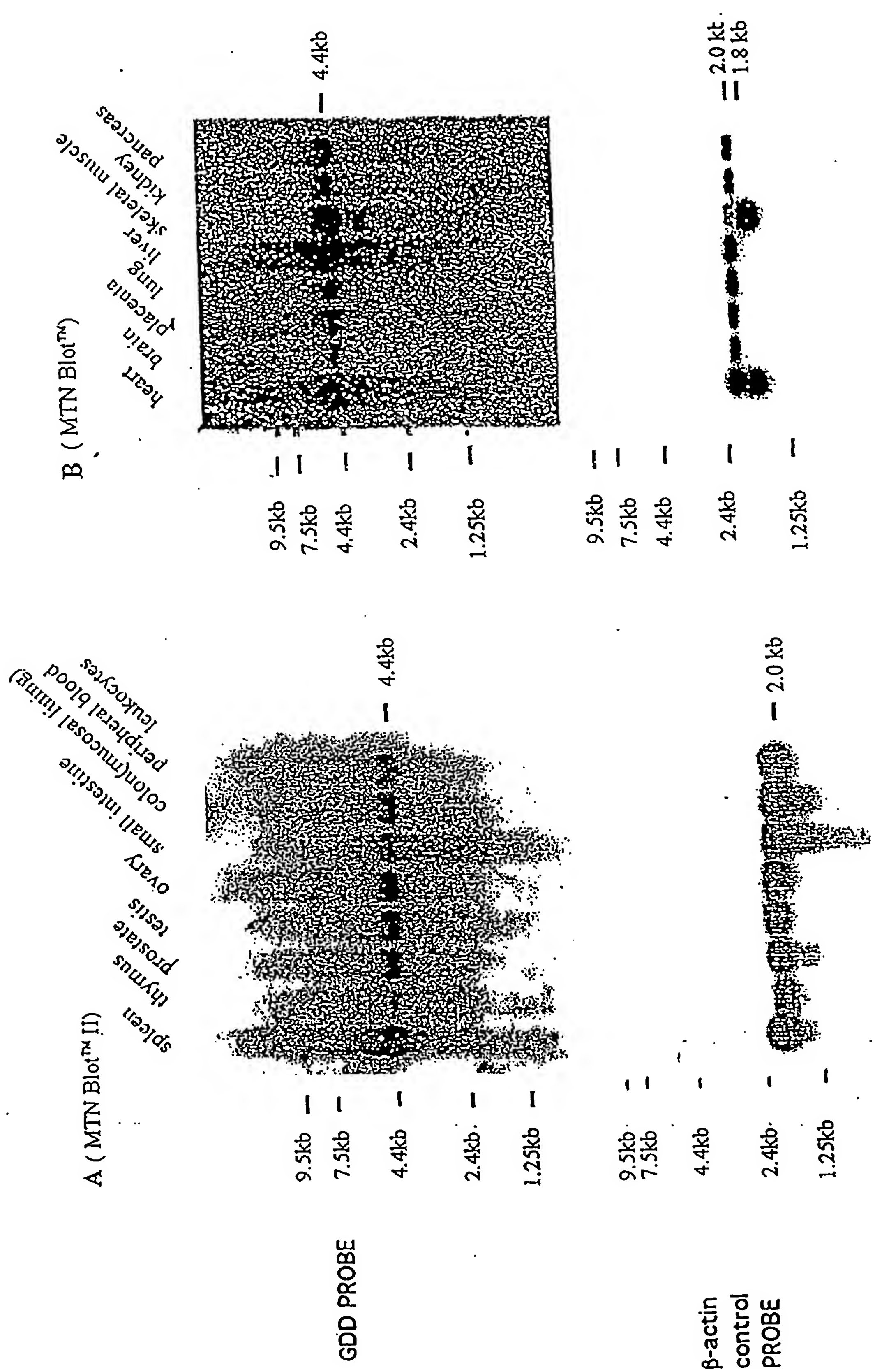
B (MTN Blot™)
heart
brain
placenta
lung
liver
skeletal muscle
kidney
pancreas
4.4kb
2.0 kb
1.8 kb
9.5kb
7.5kb
4.4kb
2.4kb
1.25kb
A (MTN Blot™ II)
spleen
thymus
prostate
testis
ovary
small intestine
colon(mucosal lining)
peripheral blood
leukocytes
4.4kb
2.0 kb
GDD PROBE
β-actin
control
PROBE

FIGURE 7

m8Ldpp9aa gap.txt

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to: mdpp9.aa  check: 4436  from: 1  to: 847

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 Percent Similarity: 94.215   Percent Identity: 90.555

hdpp9.aa x mdpp9.aa       October  5, 19101 16:00  ..

                                   .
                                   .
                                   .

 51 SHACSWNGGSLDPLEGTPALLRSAERLMRKVKKLRLDKENTGSWRSFSLN 100

  1 .................................................P 1

101 SEGAERMATTGTPTADRGDAAATDDPAARFQVQKHSWDGLRSIIHGSRKY 150
    |::::||. .|....:...|:. ||.|||| ||||||||||||||||||
  2 SQEPQRMC.SGVSPVEQVAAGDMDDTAARFCVQKHSWDGLRSIIHGSRKS 50

151 SGLIVNKAPHDFQFVQKTDESGPHSHRLYYLGMPYGSRENSLLYSEIPKK 200
    |||||.|||||||||||.||||||||||||||||||||||||||||||||
 51 SGLIVSKAPHDFQFVQKPDESGPHSHRLYYLGMPYGSRENSLLYSEIPKK 100

201 VRKEALLLLSWKQMLDHFQATPHHGVYSREEELLRERKRLGVFGITSYDF 250
    ||||||||||||||||||||||||||||||||||||||||||||||||||
101 VRKEALLLLSWKQMLDHFQATPHHGVYSREEELLRERKRLGVFGITSYDF 150
```

FIGURE 8

```
              .         .         .         .         .
251 HSESGLFLFQASNSLFHCRDGGKNGFMVSPMKPLEIKTQCSGPRMDPKIC 300
    ||||||||||||||||||||||||||||||||||||||||||||||||||
151 HSESGLFLFQASNSLFHCRDGGKNGFMVSPMKPLEIKTQCSGPRMDPKIC 200
              .         .         .         .         .
301 PADPAFFSFNNNSDLWVANIETGEERRLTFCHQGLSNVLDDPKSAGVATF 350
    ||||||||| |||||||||||||||||||||||| ..|||:|||||||||
201 PADPAFFSFINNSDLWVANIETGEERRLTFCHQGSAGVLDNPKSAGVATF 250
              .         .         .         .         .
351 VIQEEFDRFTGYWWCPTASWEGSQGLKTLRILYEEVDESEVEVIHVPSPA 400
    |||||||||||:|||||||||||:||||||||||||||||||||||||||
251 VIQEEFDRFTGCWWCPTASWEGSEGLKTLRILYEEVDESEVEVIHVPSPA 300
              .         .         .         .         .
401 LEERKTDSYRYPRTGSKNPKIALKLAEFQTDSQGKIVSTQEKELVQPFSS 450
    |||||||||||||||||||||||||||:||| ||||||. ||||||||||
301 LEERKTDSYRYPRTGSKNPKIALKLAELQTDHQGKIVSSCEKELVQPFSS 350
              .         .         .         .         .
451 LFPKVEYIARAGWTRDGKYAWAMFLDRPQQWLQLVLLPPALFIPSTENEE 500
    ||||||||||||||||||||||||||||||:|||||||||||||..|.|.
351 LFPKVEYIARAGWTRDGKYAWAMFLDRPQQRLQLVLLPPALFIPAVESEA 400
              .         .         .         .         .
501 QRLASARAVPRNVQPYVVYEEVTNVWINVHDIFYPFPQSEGEDELCFLRA 550
    || |.|||||:||||:|:|||||||||||||||.||||.||::::|||||
401 QRQAAARAVPKNVQPFVIYEEVTNVWINVHDIFHPFPQAEGQQDFCFLRA 450
              .         .         .         .         .
551 NECKTGFCHLYKVTAVLKSQGYDWSEPFSPGEDEFKCPIKEEIALTSGEW 600
    |||||||||||:||. ||..:|||.||:||.|:|||||||||:|||||||
451 NECKTGFCHLYRVTVELKTKDYDWTEPLSPTEGEFKCPIKEEVALTSGEW 500
              .         .         .         .         .
601 EVLARHGSKIWVNEETKLVYFQGTKDTPLEHHLYVVSYEAAGEIVRLTTP 650
    |||.||||||||||:|||||||||||||||||||||||||.|||||.|||
```

FIGURE 8

```
501 EVLSRHGSKIWVNEQTKLVYFQGTKDTPLEHHLYVVSYESAGEIVRLTTL 550
             .         .         .         .         .
651 GFSHSCSMSQNFDMFVSHYSSVSTPPCVHVYKLSGPDDDPLHKQPRFWAS 700
    ||||||||||.|||||||||||||||||||||||||||||||||||||||
551 GFSHSCSMSQSFDMFVSHYSSVSTPPCVHVYKLSGPDDDPLHKQPRFWAS 600
             .         .         .         .         .
701 MMEAASCPPDYVPPEIFHFHTRSDVRLYGMIYKPHALQPGKKHPTVLFVY 750
    |||||.||||||||||||||||.||.|||||||||.|||||:||||||||
601 MMEAANCPPDYVPPEIFHFHTRADVQLYGMIYKPHTLQPGRKHPTVLFVY 650
             .         .         .         .         .
751 GGPQVQLVNNSFKGIKYLRLNTLASLGYAVVVIDGRGSCQRGLRFEGALK 800
    |||||||||||||||||||||||||||||||||||||||||||:||||||
651 GGPQVQLVNNSFKGIKYLRLNTLASLGYAVVVIDGRGSCQRGLHFEGALK 700
             .         .         .         .         .
801 NQMGQVEIEDQVEGLQFVAEKYGFIDLSRVAIHGWSYGGFLSLMGLIHKP 850
    |||||||||||||||:||||||||||||||||||||||||||||||||||
701 NQMGQVEIEDQVEGLQYVAEKYGFIDLSRVAIHGWSYGGFLSLMGLIHKP 750
             .         .         .         .         .
851 QVFKVAIAGAPVTVWMAYDTGYTERYMDVPENNQHGYEAGSVALHVEKLP 900
    ||||||||||||||||||||||||||||||||||:|||||||||||||||
751 QVFKVAIAGAPVTVWMAYDTGYTERYMDVPENNQQGYEAGSVALHVEKLP 800
             .         .         .         .         .
901 NEPNRLLILHGFLDENVHFFHTNFLVSQLIRAGKPYQLQIYPNERHSIRC 950
    |||||||||||||||||||||||||||||||||||||||:      |: .
801 NEPNRLLILHGFLDENVHFFHTNFLVSQLIRAGKPYQLQV.....ASVTT 845
             .
951 PESGEHYEVTLLHFLQEYL 969
    |:
846 PQ................. 847
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FIGURE 8

mbL dpp9 dragg.b

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 to: mdpp9.dna  check: 672  from: 1  to: 2873

/home/rpag02/Cathy/tedfamily/PATENT/mdpp9.dna  [Unknown form]

 Symbol comparison table: /dbase/gcg/gcgcore/data/rundata/nwsgapdna.cmp
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       Length Weight:  0.300   Average Mismatch:  0.000

             Quality: 2166.5             Length:   3172
               Ratio:  0.754               Gaps:      2
  Percent Similarity: 80.637   Percent Identity: 80.637

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                                 .
                                 .
                                 .

                 .         .         .         .         .
     251 TGCGCCTGGACAAGGAGAACACCGGAAGTTGGAGAAGCTTCTCGCTGAAT 300
                                                        |
       1 ..............................................GCCA 4
                 .         .         .         .         .
     301 TCCGAGGGGGCTGAGAGGATGGCCACCACCGGGACCCCAACGGCCGACCG 350
         ||  ||| | |  ||||||||     || ||||  | | |  | ||  | 
       5 TCACAGGAGCCCCAGAGGATG...TGCAGCGGGGTCTCCCCAGTTGAGCA 51
                 .         .         .         .         .
     351 AGGCGACGCAGCCGCCACAGATGACCCGGCCGCCCGCTTCCAGGTGCAGA 400
          |  | |||||  | ||  |||||| |||| || ||||||   |||||||
      52 GGTGGCCGCAGGGGACATGGATGACACGGCAGCACGCTTCTGTGTGCAGA 101
```

FIGURE 9

```
401 AGCACTCGTGGGACGGGCTCCGGAGCATCATCCACGGCAGCCGCAAGTAC 450
102 AGCACTCGTGGGATGGGCTGCGTAGCATTATCCACGGCAGTCGCAAGTCC 151

451 TCGGGCCTCATTGTCAACAAGGCGCCCCACGACTTCCAGTTTGTGCAGAA 500
152 TCGGGCCTCATTGTCAGCAAGGCCCCCCACGACTTCCAGTTTGTGCAGAA 201

501 GACGGATGAGTCTGGGCCCCACTCCCACCGCCTCTACTACCTGGGAATGC 550
202 GCCTGACGAGTCTGGCCCCCACTCTCACCGTCTCTATTACCTCGGAATGC 251

551 CATATGGCAGCCGGGAGAACTCCCTCCTCTACTCTGAGATTCCCAAGAAG 600
252 CTTACGGCAGCCGTGAGAACTCCCTCCTCTACTCCGAGATCCCCAAGAAA 301

601 GTCCGGAAAGAGGCTCTGCTGCTCCTGTCCTGGAAGCAGATGCTGGATCA 650
302 GTGCGGAAGGAGGCCCTGCTGCTGCTGTCCTGGAAGCAGATGCTGGACCA 351

651 TTTCCAGGCCACGCCCCACCATGGGGTCTACTCTCGGGAGGAGGAGCTGC 700
352 CTTCCAGGCCACACCCCACCATGGTGTCTACTCCCGAGAGGAGGAGCTAC 401

701 TGAGGGAGCGGAAACGCCTGGGGGTCTTCGGCATCACCTCCTACGACTTC 750
402 TGCGGGAGCGCAAGCGCCTGGGCGTCTTCGGAATCACCTCTTATGACTTC 451

751 CACAGCGAGAGTGGCCTCTTCCTCTTCCAGGCCAGCAACAGCCTCTTCCA 800
452 CACAGTGAGAGCGGCCTCTTCCTCTTCCAGGCCAGCAATAGCCTGTTCCA 501

801 CTGCCGCGACGGCGGCAAGAACGGCTTCATGGTGTCCCCTATGAAACCGC 850
```

FIGURE 9

```
 502 CTGCAGGGATGGTGGCAAGAATGGCTTTATGGTGTCCCCGATGAAGCCAC 551

 851 TGGAAATCAAGACCCAGTGCTCAGGGCCCCGGATGGACCCCAAAATCTGC 900
     |||| |||||||| ||||| || ||||| || |||||||||||||||||
 552 TGGAGATCAAGACTCAGTGTTCTGGGCCACGCATGGACCCCAAAATCTGC 601

 901 CCTGCCGACCCTGCCTTCTTCTCCTTCAACAATAACAGCGACCTGTGGGT 950
     || || ||||||||||||| ||||||| ||| ||||| || ||||||||
 602 CCCGCAGACCCTGCCTTCTTTCCTTCATCAACAACAGTGATCTGTGGGT 651

 951 GGCCAACATCGAGACAGGCGAGGAGCGGCGGCTGACCTTCTGCCACCAAG 1000
     ||| ||||||||||| || ||||| |||||||| |||||||| ||||| |
 652 GGCAAACATCGAGACTGGGGAGGAACGGCGGCTCACCTTCTGTCACCAGG 701

1001 GTTTATCCAATGTCCTGGATGACCCCAAGTCTGCGGGTGTGGCCACCTTC 1050
     ||| | |    |||||||||  | ||||| || || || |||||||||||
 702 GTTCAGCTGGTGTCCTGGACAATCCCAAATCAGCAGGCGTGGCCACCTTT 751

1051 GTCATACAGGAAGAGTTCGACCGCTTCACTGGGTACTGGTGGTGCCCCAC 1100
     ||||| ||||| ||||||||||||||||||||| ||||||||||||||
 752 GTCATCCAGGAGGAGTTCGACCGCTTCACTGGGTGCTGGTGGTGCCCCAC 801

1101 AGCCTCCTGGGAAGGTTCAGAGGGCCTCAAGACGCTGCGAATCCTGTATG 1150
      ||||| |||||||| || || || |||||||||||||| ||||| ||||
 802 GGCCTCTTGGGAAGGCTCCGAAGGTCTCAAGACGCTGCGCATCCTATATG 851

1151 AGGAAGTCGATGAGTCCGAGGTGGAGGTCATTCACGTCCCCTCTCCTGCG 1200
     ||||||| || ||||| || |||||||||||||| || ||||| || ||
 852 AGGAAGTGGACGAGTCTGAAGTGGAGGTCATTCATGTGCCCTCCCCCGCC 901

1201 CTAGAAGAAAGGAAGACGGACTCGTATCGGTACCCCAGGACAGGCAGCAA 1250
     || || || |||||||||||||| || || |||||||||||||||||||
 902 CTGGAGGAGAGGAAGACGGACTCCTACCGCTACCCCAGGACAGGCAGCAA 951
```

FIGURE 9

```
1251 GAATCCCAAGATTGCCTTGAAACTGGCTGAGTTCCAGACTGACAGCCAGG 1300
     ||| |||||||||||| |||| ||||||||| ||||||| |||   ||||
 952 GAACCCCAAGATTGCCCTGAAGCTGGCTGAGCTCCAGACGGACCATCAGG 1001

1301 GCAAGATCGTCTCGACCCAGGAGAAGGAGCTGGTGCAGCCCTTCAGCTCG 1350
     |||| ||||| || | |   |||||||| ||||| ||||| ||||||||
1002 GCAAAATCGTGTCAAGCTGCGAGAAGGAACTGGTACAGCCATTCAGCTCC 1051

1351 CTGTTCCCGAAGGTGGAGTACATCGCCAGGGCCGGGTGGACCCGGGATGG 1400
     || ||||| || ||||||||||||||| |||| || ||||| ||||| ||
1052 CTTTTCCCCAAAGTGGAGTACATCGCCCGGGCTGGCTGGACACGGGACGG 1101

1401 CAAATACGCCTGGGCCATGTTCCTGGACCGGCCCCAGCAGTGGCTCCAGC 1450
     |||||| ||||||||||||||||||||||| ||||||||  |||| ||||
1102 CAAATATGCCTGGGCCATGTTCCTGGACCGTCCCCAGCAACGGCTTCAGC 1151

1451 TCGTCCTCCTCCCCCCGGCCCTGTTCATCCCGAGCACAGAGAATGAGGAG 1500
     | |||||||| ||||| || || |||||||||  |   |||| |||||
1152 TTGTCCTCCTGCCCCCTGCTCTCTTCATCCCGGCCGTTGAGAGTGAGGCC 1201

1501 CAGCGGCTAGCCTCTGCCAGAGCTGTCCCCAGGAATGTCCAGCCGTATGT 1550
     |||||||  ||  |||||||||| ||||||| |||||| ||||| | |||
1202 CAGCGGCAGGCAGCTGCCAGAGCCGTCCCCAAGAATGTGCAGCCCTTTGT 1251

1551 GGTGTACGAGGAGGTCACCAACGTCTGGATCAATGTTCATGACATCTTCT 1600
       | || || ||||||||||| ||||||||||| || || |||||||||
1252 CATCTATGAAGAAGTCACCAATGTCTGGATCAACGTCCACGACATCTTCC 1301

1601 ATCCCTTCCCCCAATCAGAGGGAGAGGACGAGCTCTGCTTTCTCCGCGCC 1650
     | || || || ||  | |||||  || | ||  | || || || || |||
1302 ACCCGTTTCCTCAGGCTGAGGGCCAGCAGGACTTTTGTTTCCTTCGTGCC 1351

1651 AATGAATGCAAGACCGGCTTCTGCCATTTGTACAAAGTCACCGCCGTTTT 1700
     ||.||||||||||| |||||||||||  ||||||  ||||| |  |   |
1352 AACGAATGCAAGACTGGCTTCTGCCACCTGTACAGGGTCACAGTGGAACT 1401
```

FIGURE 9

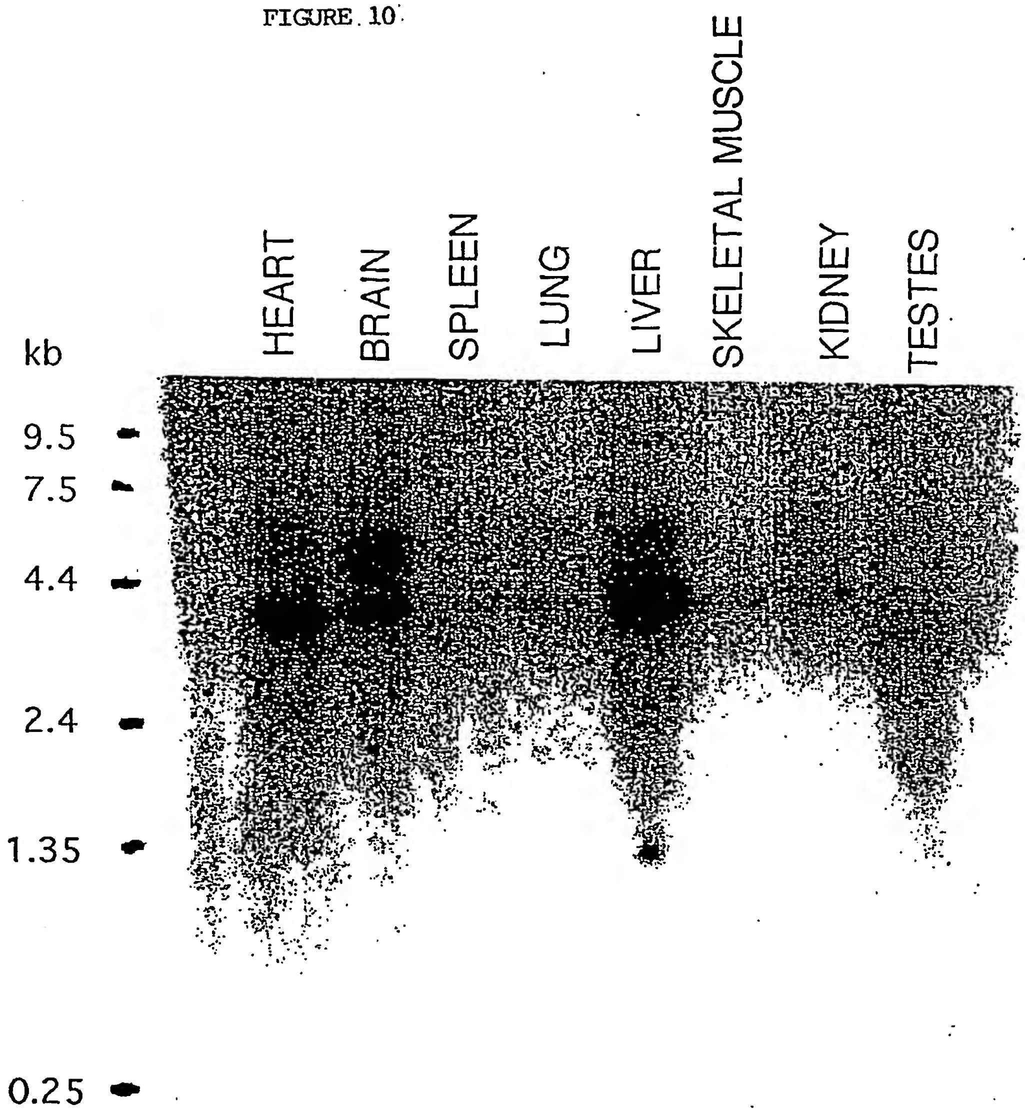
```
1701 AAAATCCCAGGGCTACGATTGGAGTGAGCCCTTCAGCCCCGGGGAAGATG 1750
1402 TAAAACCAAGGACTATGACTGGACGGAACCCCTCAGCCCTACAGAAGGTG 1451

1751 AATTTAAGTGCCCCATTAAGGAAGAGATTGCTCTGACCAGCGGTGAATGG 1800
1452 AGTTTAAGTGCCCCATCAAGGAGGAGGTCGCCCTGACCAGTGGCGAGTGG 1501

1801 GAGGTTTTGGCGAGGCACGGCTCCAAGATCTGGGTCAATGAGGAGACCAA 1850
1502 GAGGTCTTGTCGAGGCATGGCTCCAAGATCTGGGTCAACGAGCAGACGAA 1551

1851 GCTGGTGTACTTCCAGGGCACCAAGGACACGCCGCTGGAGCACCACCTCT 1900
1552 GCTGGTGTACTTTCAAGGTACAAAGGACACACCGCTGGAACATCACCTCT 1601

1901 ACGTGGTCAGCTATGAGGCGGCCGGCGAGATCGTACGCCTCACCACGCCC 1950
1602 ATGTGGTCAGCTACGAGTCAGCAGGCGAGATCGTGCGGCTCACCACGCTC 1651

1951 GGCTTCTCCCATAGCTGCTCCATGAGCCAGAACTTCGACATGTTCGTCAG 2000
1652 GGCTTCTCCCACAGCTGCTCCATGAGCCAGAGCTTCGACATGTTCGTGAG 1701

2001 CCACTACAGCAGCGTGAGCACGCCGCCCTGCGTGCACGTCTACAAGCTGA 2050
1702 TCACTACAGCAGTGTGAGCACGCCACCCTGTGTACATGTGTACAAGCTGA 1751

2051 GCGGCCCCGACGACGACCCCCTGCACAAGCAGCCCCGCTTCTGGGCTAGC 2100
1752 GCGGCCCCGATGATGACCCACTGCACAAGCAACCACGCTTCTGGGCCAGC 1801

2101 ATGATGGAGGCAGCCAGCTGCCCCCCGGATTATGTTCCTCCAGAGATCTT 2150
1802 ATGATGGAGGCAGCCAATTGCCCCCCAGACTATGTGCCCCCTGAGATCTT 1851
```

FIGURE 9

```
2151 CCATTTCCACACGCGCTCGGATGTGCGGCTCTACGGCATGATCTACAAGC 2200
     ||| |||||||| ||  | || |||| |||||||||||||||||||||||
1852 CCACTTCCACACCCGTGCAGACGTGCAGCTCTACGGCATGATCTACAAGC 1901

2201 CCCACGCCTTGCAGCCAGGGAAGAAGCACCCCACCGTCCTCTTTGTATAT 2250
     | ||| || |||| || |||| ||||||||||| || |||||||| |||
1902 CACACACCCTGCAACCTGGGAGGAAGCACCCCACTGTGCTCTTTGTCTAT 1951

2251 GGAGGCCCCCAGGTGCAGCTGGTGAATAACTCCTTCAAAGGCATCAAGTA 2300
     || ||||| ||||||||| ||||||| |||||||| || |||||||| ||
1952 GGGGGCCCACAGGTGCAGTTGGTGAACAACTCCTTTAAGGGCATCAAATA 2001

2301 CTTGCGGCTCAACACACTGGCCTCCCTGGGCTACGCCGTGGTTGTGATTG 2350
     | ||||||| || |||||||| ||| ||||||| || ||||| ||||| |
2002 CCTGCGGCTAAATACACTGGCATCCTTGGGCTATGCTGTGGTGGTGATCG 2051

2351 ACGGCAGGGGCTCCTGTCAGCGAGGGCTTCGGTTCGAAGGGGCCCTGAAA 2400
     | ||  |||||||||||||||| || || |  ||||| ||||||||||||
2052 ATGGTCGGGGCTCCTGTCAGCGGGGCCTGCACTTCGAGGGGGCCCTGAAA 2101

2401 AACCAAATGGGCCAGGTGGAGATCGAGGACCAGGTGGAGGGCCTGCAGTT 2450
     || |||||||||||||||||||| |||||||||||||| ||| ||||||
2102 AATCAAATGGGCCAGGTGGAGATTGAGGACCAGGTGGAAGGCTTGCAGTA 2151

2451 CGTGGCCGAGAAGTATGGCTTCATCGACCTGAGCCGAGTTGCCATCCATG 2500
     |||||| ||||||||||||||||| ||| |||||||||| ||||||||||
2152 CGTGGCTGAGAAGTATGGCTTCATTGACTTGAGCCGAGTCGCCATCCATG 2201

2501 GCTGGTCCTACGGGGGCTTCCTCTCGCTCATGGGGCTAATCCACAAGCCC 2550
     ||||||||||||| ||||||||||| ||||||||||| |||||||||||
2202 GCTGGTCCTACGGCGGCTTCCTCTCACTCATGGGGCTCATCCACAAGCCA 2251

2551 CAGGTGTTCAAGGTGGCCATCGCGGGTGCCCCGGTCACCGTCTGGATGGC 2600
     || ||||||||||| ||||| ||||| || || ||||| || ||||||||
```

FIGURE 9

FIGURE. 10



Rat Multiple Tissue Northern Blot hybridised with a human DPP9 probe of 2,589 bases. The hybridisation was carried out overnight at 60^{O} C.

```
2252 CAAGTGTTCAAGGTAGCCATTGCGGGCGCTCCTGTCACTGTGTGGATGGC 2301
              .         .         .         .         .
2601 CTACGACACAGGGTACACTGAGCGCTACATGGACGTCCCTGAGAACAACC 2650
     ||| |||||||||||||| || || |||||||| ||||| || || ||||
2302 CTATGACACAGGGTACACGGAACGATACATGGATGTCCCCGAAAATAACC 2351
              .         .         .         .         .
2651 AGCACGGCTATGAGGCGGGTTCCGTGGCCCTGCACGTGGAGAAGCTGCCC 2700
     |||| ||||||||||| || || || |||||||| |||||||||||||||
2352 AGCAAGGCTATGAGGCAGGGTCTGTAGCCCTGCATGTGGAGAAGCTGCCC 2401
              .         .         .         .         .
2701 AATGAGCCCAACCGCTTGCTTATCCTCCACGGCTTCCTGGACGAAAACGT 2750
     |||||||| |||||| |||||||||||||||||||||||||||| |||||
2402 AATGAGCCTAACCGCCTGCTTATCCTCCACGGCTTCCTGGACGAGAACGT 2451
              .         .         .         .         .
2751 GCACTTTTTCCACACAAACTTCCTCGTCTCCCAACTGATCCGAGCAGGGA 2800
      ||||| ||||||||||| ||||| || ||||| |||||||||||||| |
2452 TCACTTCTTCCACACAAATTTCCTGGTGTCCCAGCTGATCCGAGCAGGAA 2501
              .         .         .         .         .
2801 AACCTTACCAGCTCCAGAT..CTACCCCAACGAGAGACACAGTATTCGCT 2848
     | || |||||||| ||| |  |  |    || | | |        | |  |
2502 AGCCATACCAGCTTCAGGTTGCATCAGTGACAACACCTCAGTGACTACCC 2551
              .         .         .         .         .
2849 GCCCCGAGTCGGGCGAGCACTATGAAGTCACGTTACTGCACTTTCTACAG 2898
       | | |      |       |||||  ||| |  || ||        ||
2552 CTCACTAAGACCCCAGTTTTGATGAACCCACTTGGCTACAGGCATGGGAG 2601
              .         .         .         .         .
2899 GAATACCTCTGAGCCTGCCCACCGGGAGCCGCCACATCACAGCACAAGTG 2948
          ||         |    ||  |||| |   | | |  |
2602 TGCCCCCCAATGATTAGAGACCCAAGAGCAGTTGCCTGAGGGAGAGGACA 2651
              .         .         .         .         .
2949 GCTGCAGCCTCCGCGGGGAACCAGGCGGGAGGGACTGAGTGGCCCGCGGG 2998
       |  ||   | |    ||| |   |   | |       | ||   ||
2652 TTTAAAGGTCCAGGACTGAATCTACCCAAACGAGAGACATAGCATCCGCT 2701
              .         .         .         .         .
2999 CC................................................ 3000
      |
2702 GCCGCGAGTCCGGAGAGCATTACGAGGTGACGCTGCTGCACTTTCTGCAG 2751
```

FIGURE 9

DPP9 PCR products.
Lane 2; generated from CEM cell line RNA using DPP9 primers 22F and 3' end.
Lane 4; the same primers with XbaI sites on th ends.

FIGURE 11

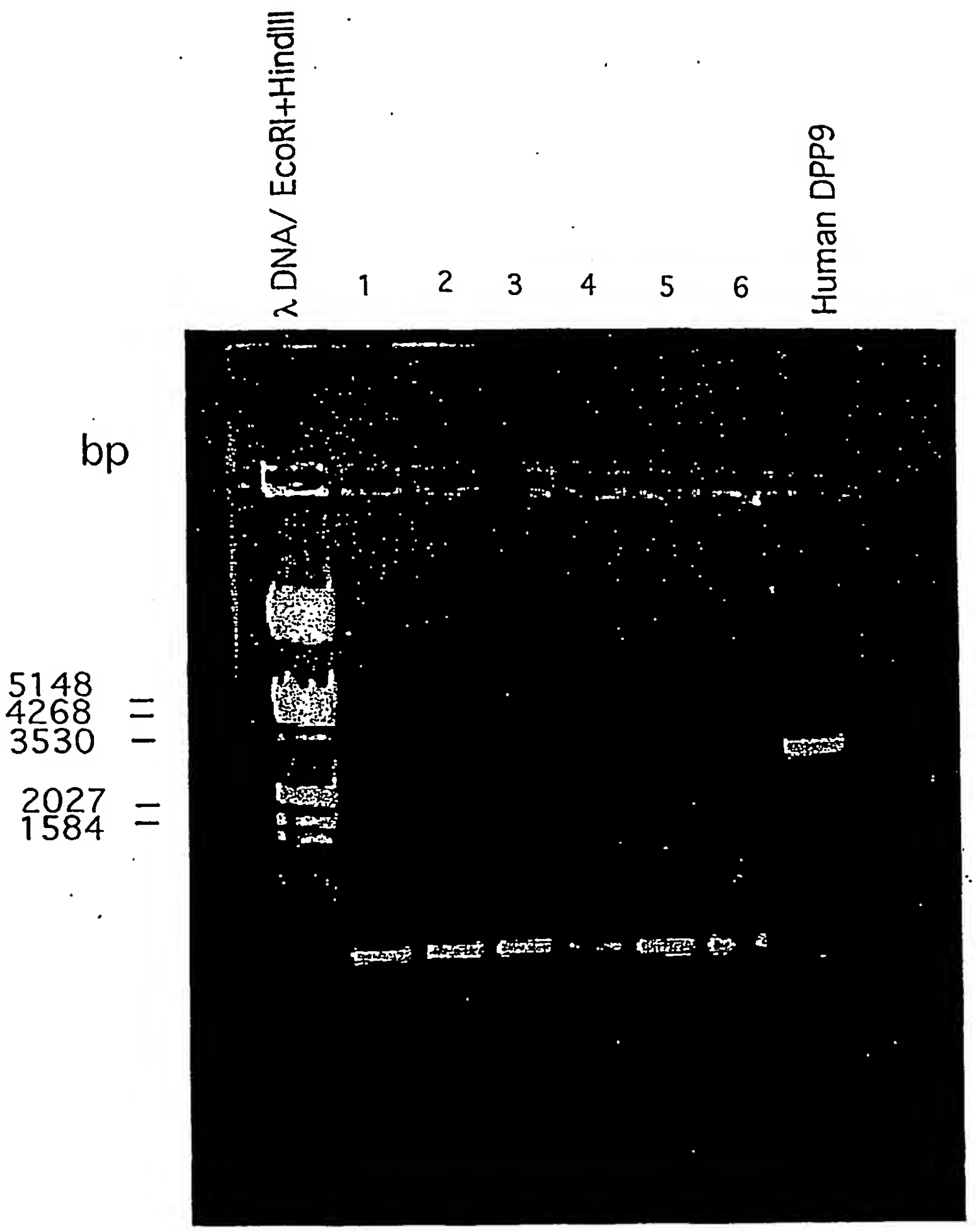


Figure showing DPP9 PCR products from liver of six mice (numbered 1 to 6) and the largest human DPP9 fragment.

FIGURE 12

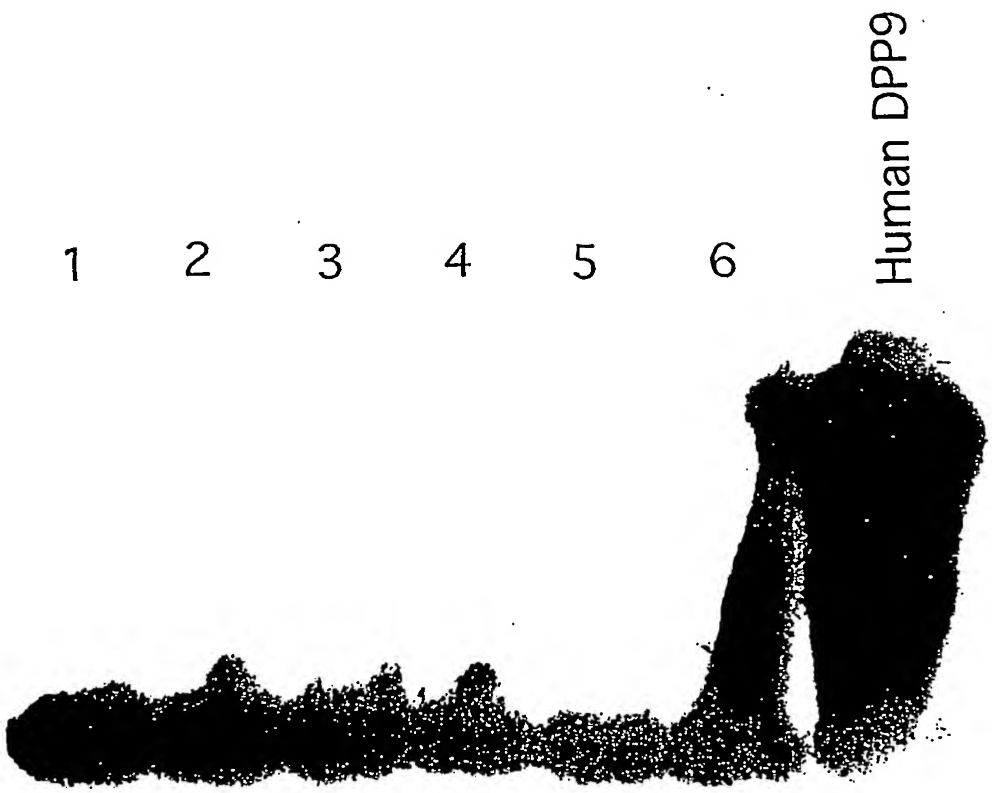


FIGURE 12.

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<160> 8

<170> PatentIn version 3.1

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tccggccgcc gccccacgtc ccggtctgtg tcccacgcct gcagctggaa tggaggctct 180

ctggaccctt tagaaggcac ccctgccctc ctgaggtcag ctgagcggtt aatgcggaag 240

gttaagaaac tgcgcctgga caaggagaac accggaagtt ggagaagctt ctcgctgaat 300

tccgaggggg ctgagaggat ggccaccacc gggaccccaa cggccgaccg aggcgacgca 360

gccgccacag atgacccggc cgcccgcttc caggtgcaga agcactcgtg ggacgggctc 420

cggagcatca tccacggcag ccgcaagtac tcgggcctca ttgtcaacaa ggcgccccac 480

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gtccggaaag aggctctgct gctcctgtcc tggaagcaga tgctggatca tttccaggcc 660

acgccccacc atggggtcta ctctcgggag gaggagctgc tgagggagcg gaaacgcctg

720

ggggtcttcg gcatcacctc ctacgacttc cacagcgaga gtggcctctt cctcttccag
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Ser Val Ser His Ala Cys Ser Trp Asn Gly Gly Ser Leu Asp Pro Leu
50 55 60

Glu Gly Thr Pro Ala Leu Leu Arg Ser Ala Glu Arg Leu Met Arg Lys
65 70 75 80

Val Lys Lys Leu Arg Leu Asp Lys Glu Asn Thr Gly Ser Trp Arg Ser
85 90 95

Phe Ser Leu Asn Ser Glu Gly Ala Glu Arg Met Ala Thr Thr Gly Thr
100 105 110

Pro Thr Ala Asp Arg Gly Asp Ala Ala Ala Thr Asp Asp Pro Ala Ala
115 120 125

Arg Phe Gln Val Gln Lys His Ser Trp Asp Gly Leu Arg Ser Ile Ile
    130   135   140

His Gly Ser Arg Lys Tyr Ser Gly Leu Ile Val Asn Lys Ala Pro His
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Asp Phe Gln Phe Val Gln Lys Thr Asp Glu Ser Gly Pro His Ser His
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Arg Leu Tyr Tyr Leu Gly Met Pro Tyr Gly Ser Arg Glu Asn Ser Leu
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Leu Tyr Ser Glu Ile Pro Lys Lys Val Arg Lys Glu Ala Leu Leu Leu
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Gly Val Tyr Ser Arg Glu Glu Glu Leu Leu Arg Glu Arg Lys Arg Leu
225   230   235   240

Gly Val Phe Gly Ile Thr Ser Tyr Asp Phe His Ser Glu Ser Gly Leu
                245   250   255

Phe Leu Phe Gln Ala Ser Asn Ser Leu Phe His Cys Arg Asp Gly Gly
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Lys Asn Gly Phe Met Val Ser Pro Met Lys Pro Leu Glu Ile Lys Thr
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Gln Cys Ser Gly Pro Arg Met Asp Pro Lys Ile Cys Pro Ala Asp Pro
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Ala Phe Phe Ser Phe Asn Asn Asn Ser Asp Leu Trp Val Ala Asn Ile
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Glu Thr Gly Glu Glu Arg Arg Leu Thr Phe Cys His Gln Gly Leu Ser
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Gln Gly Lys Ile Val Ser Thr Gln Glu Lys Glu Leu Val Gln Pro Phe
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Val His Asp Ile Phe Tyr Pro Phe Pro Gln Ser Glu Gly Glu Asp Glu
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Tyr Lys Val Thr Ala Val Leu Lys Ser Gln Gly Tyr Asp Trp Ser Glu
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Pro Phe Ser Pro Gly Glu Asp Glu Phe Lys Cys Pro Ile Lys Glu Glu
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Ile Ala Leu Thr Ser Gly Glu Trp Glu Val Leu Ala Arg His Gly Ser
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Lys Ile Trp Val Asn Glu Glu Thr Lys Leu Val Tyr Phe Gln Gly Thr
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Lys Asp Thr Pro Leu Glu His His Leu Tyr Val Val Ser Tyr Glu Ala
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Ala Gly Glu Ile Val Arg Leu Thr Thr Pro Gly Phe Ser His Ser Cys
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Ser Met Ser Gln Asn Phe Asp Met Phe Val Ser His Tyr Ser Ser Val
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Ser Thr Pro Pro Cys Val His Val Tyr Lys Leu Ser Gly Pro Asp Asp
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Asp Pro Leu His Lys Gln Pro Arg Phe Trp Ala Ser Met Met Glu Ala
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Ala Ser Cys Pro Pro Asp Tyr Val Pro Pro Glu Ile Phe His Phe His
705                 710                 715                 720

Thr Arg Ser Asp Val Arg Leu Tyr Gly Met Ile Tyr Lys Pro His Ala
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Leu Gln Pro Gly Lys Lys His Pro Thr Val Leu Phe Val Tyr Gly Gly
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Pro Gln Val Gln Leu Val Asn Asn Ser Phe Lys Gly Ile Lys Tyr Leu
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Arg Leu Asn Thr Leu Ala Ser Leu Gly Tyr Ala Val Val Val Ile Asp
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Gly Arg Gly Ser Cys Gln Arg Gly Leu Arg Phe Glu Gly Ala Leu Lys
785                 790                 795                 800

Asn Gln Met Gly Gln Val Glu Ile Glu Asp Gln Val Glu Gly Leu Gln
                805                 810                 815

Phe Val Ala Glu Lys Tyr Gly Phe Ile Asp Leu Ser Arg Val Ala Ile
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His Gly Trp Ser Tyr Gly Gly Phe Leu Ser Leu Met Gly Leu Ile His
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Lys Pro Gln Val Phe Lys Val Ala Ile Ala Gly Ala Pro Val Thr Val
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Trp Met Ala Tyr Asp Thr Gly Tyr Thr Glu Arg Tyr Met Asp Val Pro
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Glu Asn Asn Gln His Gly Tyr Glu Ala Gly Ser Val Ala Leu His Val
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Glu Lys Leu Pro Asn Glu Pro Asn Arg Leu Leu Ile Leu His Gly Phe
            900                 905                 910

Leu Asp Glu Asn Val His Phe Phe His Thr Asn Phe Leu Val Ser Gln
        915                 920                 925

Leu Ile Arg Ala Gly Lys Pro Tyr Gln Leu Gln Ile Tyr Pro Asn Glu
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Arg His Ser Ile Arg Cys Pro Glu Ser Gly Glu His Tyr Glu Val Thr
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Lys Ser Ser Gly Leu Ile Val Ser Lys Ala Pro His Asp Phe Gln Phe
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Val Gln Lys Pro Asp Glu Ser Gly Pro His Ser His Arg Leu Tyr Tyr
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Leu Gly Met Pro Tyr Gly Ser Arg Glu Asn Ser Leu Leu Tyr Ser Glu
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Ile Pro Lys Lys Val Arg Lys Glu Ala Leu Leu Leu Ser Trp Lys

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Gln Met Leu Asp His Phe Gln Ala Thr Pro His His Gly Val Tyr Ser
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Arg Glu Glu Glu Leu Leu Arg Glu Arg Lys Arg Leu Gly Val Phe Gly
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Ile Thr Ser Tyr Asp Phe His Ser Glu Ser Gly Leu Phe Leu Phe Gln
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Ala Ser Asn Ser Leu Phe His Cys Arg Asp Gly Gly Lys Asn Gly Phe
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Met Val Ser Pro Met Lys Pro Leu Glu Ile Lys Thr Gln Cys Ser Gly
180 185 190

Pro Arg Met Asp Pro Lys Ile Cys Pro Ala Asp Pro Ala Phe Phe Ser
195 200 205

Phe Ile Asn Asn Ser Asp Leu Trp Val Ala Asn Ile Glu Thr Gly Glu
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Glu Arg Arg Leu Thr Phe Cys His Gln Gly Ser Ala Gly Val Leu Asp
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Asn Pro Lys Ser Ala Gly Val Ala Thr Phe Val Ile Gln Glu Glu Phe
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Asp Arg Phe Thr Gly Cys Trp Trp Cys Pro Thr Ala Ser Trp Glu Gly
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Ser Glu Gly Leu Lys Thr Leu Arg Ile Leu Tyr Glu Glu Val Asp Glu
275 280 285

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Lys Thr Asp Ser Tyr Arg Tyr Pro Arg Thr Gly Ser Lys Asn Pro Lys

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Gln Arg Gln Ala Ala Ala Arg Ala Val Pro Lys Asn Val Gln Pro Phe
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Val Ile Tyr Glu Glu Val Thr Asn Val Trp Ile Asn Val His Asp Ile
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Ser Gly Glu Trp Glu Val Leu Ser Arg His Gly Ser Lys Ile Trp Val
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Cys Val His Val Tyr Lys Leu Ser Gly Pro Asp Asp Asp Pro Leu His
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Lys Gln Pro Arg Phe Trp Ala Ser Met Met Glu Ala Ala Asn Cys Pro
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Pro Asp Tyr Val Pro Pro Glu Ile Phe His Phe His Thr Arg Ala Asp
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Val Gln Leu Tyr Gly Met Ile Tyr Lys Pro His Thr Leu Gln Pro Gly
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Arg Lys His Pro Thr Val Leu Phe Val Tyr Gly Gly Pro Gln Val Gln
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Cys Gln Arg Gly Leu His Phe Glu Gly Ala Leu Lys Asn Gln Met Gly
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Gln Val Glu Ile Glu Asp Gln Val Glu Gly Leu Gln Tyr Val Ala Glu
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Lys Tyr Gly Phe Ile Asp Leu Ser Arg Val Ala Ile His Gly Trp Ser

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Tyr Gly Gly Phe Leu Ser Leu Met Gly Leu Ile His Lys Pro Gln Val
740 745 750

Phe Lys Val Ala Ile Ala Gly Ala Pro Val Thr Val Trp Met Ala Tyr
755 760 765

Asp Thr Gly Tyr Thr Glu Arg Tyr Met Asp Val Pro Glu Asn Asn Gln
770 775 780

Gln Gly Tyr Glu Ala Gly Ser Val Ala Leu His Val Glu Lys Leu Pro
785 790 795 800

Asn Glu Pro Asn Arg Leu Leu Ile Leu His Gly Phe Leu Asp Glu Asn
805 810 815

Val His Phe Phe His Thr Asn Phe Leu Val Ser Gln Leu Ile Arg Ala
820 825 830

Gly Lys Pro Tyr Gln Leu Gln Ile Tyr Pro Asn Glu Arg His Ser Ile
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Glu Ala Leu Leu Leu Leu Ser Trp Lys Gln Met Leu Asp His Phe Gln
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Tyr Phe Gln Gly Thr Lys Asp Thr Pro Leu Glu His His Leu Tyr Val
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INTERNATIONAL SEARCH REPORT	International application No. PCT/AU01/01388

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: C12N 9/64, 5/10, 5/12; A61K 38/43; C07K 16/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

ANGIS sequence search: sequence ID No 2, 4 and 7;
STN: File CA sequences in claim 1 part (b)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	Eur. J. Biochem, Volume 267, No.20, issued Oct 2000, C.A.Abbott et al, "Cloning , expression and chromosomal localization of a novel human dipeptidyl peptidase (DPP) IV homolog, DPP8", pages 6140-6150. See whole document but in particular abstract and sequence listings.	1-23
P,X	WO 01/19866 A1 (THE UNIVERSITY OF SYDNEY) 22 March 2001 Whole document.	1-23
P,X	GenPept accession Number AAH00970 mRNA, partial cds. Submitted 16 Nov 2000.	24, 25

☐ Further documents are listed in the continuation of Box C ☒ See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 December 2001	13 DEC 2001
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized officer **K. LEVER** Telephone No : (02) 6283 2254

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/AU01/01388**

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member	
WO	01/19866	AU	73946/00

END OF ANNEX